EXHIBIT A

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ANTICANCER, INC., a California corporation, Plaintiff, v. CELLSIGHT TECHNOLOGIES, INC. a Delaware corporation; and DOES 1-50, Defendants.	Case No.: 10 CV 2515 (JLS) (RBB) **EXPERT WITNESS REPORT OF ROBERT M. HOFFMAN, PH.D.**

I, Robert M. Hoffman, assigned to provide expert testimony on behalf of AntiCancer, Inc. ("AntiCancer") in the above-captioned action, submit this Expert Report.

1. According to Federal Rule of Civil Procedure 26(a)(2), this Expert Report discloses my opinions regarding, among other things, the infringement by CellSight Technologies, Inc. ("CellSight") of AntiCancer's U.S. Patent Nos. 6,649,159 (the "'159 patent") and 6,759,038 (the "'038 Patent") and the bases and reasons supporting my

opinions. This report sets forth the opinions I have formed based on information available as of the date below. I understand that CellSight Technologies, Inc. ("CellSight") may submit expert reports or other materials in response to this Report, and I reserve the right to review those reports and to offer additional reports as appropriate. I expect to be called to testify at trial in the above-captioned action.

2. I received my Ph.D. in Biology from Harvard University in 1971. I have done post-doctoral work at the Department of Biology at Harvard University and Harvard Medical School at Massachusetts General Hospital, where I began my work in cancer research in 1973. Also, during my post-doctoral period, I studied at the Institute of Bioorganic Chemistry in Moscow and at the Weizmann Institute in Israel.

3. I am the Founder and currently the President and CEO of AntiCancer. I am also Professor of Surgery at the University of California, San Diego, where I have been a faculty member since 1979. I have published approximately 550 scientific papers, which have been cited approximately 20,000 times. My publications have an h-index of approximately 75, an unusually high number, demonstrating the very broad and high rate of citation of my publications. I am considered among the leading world experts in cancer research and, in particular, animal models of cancer. I have published approximately 150 papers on animal models of cancer and have developed animal models of 17 different cancers, which places me in the world-leadership position in this field. My Curriculum Vitae is attached hereto as Exhibit A.

6. I have reviewed a paper published in titled "Structure-guided Engineering of Human Thymidine Kinase 2 as a Positron Emission Tomography Reporter Gene for Enhanced Phosphorylation of Non-natural Thymidine Analog Reporter Probe," which was published in the Journal of Biological Chemistry, Volume 287, No. 1, pp. 446-454 in January 2012. Among the authors of this paper is Shahriar S. Yaghoubi, who is identified in the paper as a co-founder and Chief Scientific Officer of CellSight. The paper, which I will refer to as the "Cellsight 2012 paper", is attached hereto as Exhibit B.

7. The Cellsight 2012 paper shows clear evidence of infringement of claims 1, 7, 8, and 12 of the '159 patent and claims 5, 6, and 8 of the '038 patent, as I will explain in detail below.

8. In brief, the Cellsight 2012 paper describes using various imaging methods to, among other things, track the fluorescence of yellow fluorescent protein (YFP)-labeled tumors in mice. (YFP is understood by researchers in the field, and has been construed by the court in this case, to be among various colors of fluorescent proteins which are all generally described as "GFP.") The Cellsight 2012 paper describes how the authors took a cancer cell line (the L1210 cell line) and genetically engineered it to express YFP. These cells then expressed YFP, and were injected subcutaneously into mice. These mice were then imaged *in vivo*, and the authors put dashed lines to depict a circle or elipse representing the sites and size of the YFP-expressing tumors. See Figure 2D and Figure 4A and 4B. Each of these images shows a "YFP"-labeled circle drawn around the YFP-expressing tumor.

9. **The '159 Patent.**

Claim 1 of the '159 patent reads:

1. A method to monitor the ability of a promoter to promote expression in an animal of an endogenous gene that is controlled by said promoter, which method comprises:

a) delivering, to an animal, cells containing a nucleic acid encoding a fluorophore operatively linked to the promoter of said endogenous gene whose ability to promote expression is to be analyzed; and

b) observing the presence, absence or intensity of the fluorescence generated by said fluorophore at various locations in said animal by whole-body external fluorescent optical imaging, whereby the ability of said promoter to promote expression is monitored, and wherein said fluorophore is a protein that is autofluorescent such that no substrates or cofactors are needed for it to fluoresce.

The Cellsight 2012 paper thus describes that the YFP-labeled cancer cells were subcutaneously injected into mice. In images shown in Figures 2 and 4, the authors indicate the presence of the YFP tumors within dashed lines to form a circle or ellipse and labeled "YFP." The identification of the location and size of YFP-expressing tumors must have been made possible by imaging of the YFP fluorescence.

Claims 7 and 8 of the '159 patent read:

7. The method of claim 1, wherein the animal is a mammal.

8. The method of claim 7, wherein the mammal is selected from the group consisting of a mouse, a rat, a rabbit, a cat, a dog, a pig, a cow, an ox, a sheep, a goat, a horse, a monkey and a non-human primate.

In the Yaghoubi 2012 paper, the animals used were mice, which are mammals.

Claim 12 of the '159 patent reads:

12. The method of claim 1, wherein the endogenous gene is an endogenous tumor or cancer associated gene.

In the Cellsight 2012 paper, the YFP-expressing tumor was implanted in mice and then became endogenous.

10. **The '038 Patent.**

Claim 5 of the '038 patent reads:

5. A method to monitor metastasis of a primary tumor in a subject which is a mouse, rat or rabbit which contains said primary tumor, and wherein said tumor stably expresses green fluorescent protein (GFP) in cells of said tumor when said tumor metastasizes,

wherein said subject contains said tumor that expresses GFP and wherein said subject is a genetically immunocompromised mouse, rat or rabbit, or a mouse, rat or rabbit which is syngeneic to said tumor;

which method comprises monitoring the progression of metastasis by observing the presence, absence or intensity of the fluorescence as a function of time at various locations in said subject wherein the subject is intact.

The Cellsight 2012 paper describes imaging a mouse containing a YFP-expressing tumor. Mice used are identified as "SCID" mice, which are immunocompromised. The YFP tumors are shown by dashed lines to form a circle or ellipse that identify the location and size of the YFP-expressing tumors, which means fluorescence imaging must have been used to locate and measure the size of the YFP tumors.

Claim 6 of the '038 patent reads:

6. The method of claim 5 wherein the progression of metastasis is monitored by fluorescent optical tumor imaging in the intact subject.

The Cellsight 2012 paper and images demonstrate that the researchers monitored tumor progression using fluorescence imaging of the YFP-expressing tumors.

Claim 8 of the '038 patent reads:

> **8. The method of claim 5 wherein said subject contains said tumor by virtue of injecting cells of a stably transformed tumor cell line which has been transfected with an expression vector in containing a first nucleotide sequence encoding a selection marker, both said first and second nucleotide sequences being under control of a viral promoter and wherein said cell line stably effects high level expression of said GFP in the absence of selection agent and maintains a high level expression of GFP when said cell line proliferates through multiple passages of said cell line.**

The Cellsight 2012 paper describes how the mice imaged contained tumors which were the result of injecting L1210 cells expressing YFP under control of a viral promoter.

11. This report sets forth the opinions I have formed based on information available as of the date below. It is my understanding that unknown and unidentified material may be introduced during this litigation, which may fall within my area of expertise, and I may have relevant and important opinions regarding such unknown and unidentified material. I reserve the right consistent with judicial fairness and propriety to be able to express such opinions that may be relevant and important as such material becomes known.

12. Serving as an expert witness on behalf of AntiCancer is part of my usual duties as President and CEO. I am not receiving additional compensation for the time I have spent on this litigation, nor is my usual compensation directly linked to the outcome of this or any other AntiCancer litigation.

13. I have provided testimony at trial or by deposition in the following cases within the last four (4) years: *Hoffman La-Rouche, Inc. v. Mylan Inc. and Mylan Pharmaceuticals, Inc.*, No. 09-1692 (D.N.J.), *AntiCancer, Inc. v. Cambridge Research & Instrumentation, Inc.*, Nos. 07c v97 and 07cv1004 (S.D. Cal.), and *AntiCancer v. Teco Diagnostics* No. 07cv22294 (S.D. Cal.)

I declare under penalty of perjury that the foregoing is true and correct.

Dated: March 12, 2012

Robert M. Hoffman, Ph.D.

EXHIBIT A

CURRICULUM VITAE

ROBERT M. HOFFMAN

March 2012

EXHIBIT A
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CURRICULUM VITAE

ROBERT M. HOFFMAN

OFFICES:

AntiCancer, Inc.
7917 Ostrow Street
San Diego, California 92111
TEL: (858) 654-2555
FAX: (858) 268-4175

Department of Surgery
University of California, San Diego
Medical Center
200 West Arbor Drive
San Diego, California 92103-8402
TEL: (619) 543-6890
FAX: (619) 543-3763

BIRTH DATE:

June 19, 1944
Greenwich, Connecticut

EDUCATION:

Ph.D. (Biology) 1971
Harvard University
Cambridge, Massachusetts

B.A. (Biology) 1965
State University of New York
Buffalo, New York

PRESENT POSITIONS:

President, Chairman of Board and CEO 1984-present
AntiCancer, Inc.
San Diego, California

Professor 1995-present
Department of Surgery
University of California, San Diego
Medical Center
200 West Arbor Drive
San Diego, California 92103-8220

EXHIBIT A
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MAJOR RESEARCH ACCOMPLISHMENTS:

1) I was the first to discover a mutant in energy metabolism:

- Hoffman, R.M., and Raper, J.R. Genetic restriction of energy conservation in Schizophyllum. Science **171**, 418-419, 1971

2) I was the first to demonstrate altered DNA methylation in human cancer:

- Diala, E.S. and Hoffman, R.M. Hypomethylation of HeLa cell DNA and the absence of 5-methylcytosine in SV40 and adenovirus (type 2) DNA: analysis by HPLC. Biochem. Biophys. Res. Commun. **107**, 19-26, 1982.
- Diala, E.S., Cheah, M.S.C., Rowitch, D. and Hoffman, R.M. Extent of DNA methylation in human tumor cells. J. Natl. Cancer Inst. **71**, 755-764, 1983.

3) I was the first to demonstrate altered DNA methylation in an oncogene:

- Cheah, M.S., Wallace, C.D. and Hoffman, R.M. Hypomethylation of DNA in human cancer cells: a site-specific change in the c-myc oncogene. J. Natl. Cancer Inst. **73,** 1057-1065, 1984.

4) I was the first to demonstrate altered general methylation in cancer:

- Hoffman, R.M. and Erbe, RW. High *in vivo* rates of methionine biosynthesis in transformed human and malignant rat cells auxotrophic for methionine. Proc. Natl. Acad. Sci. USA **73**, 1523-1527, 1976.
- Hoffman, R.M., Jacobsen, S.J. and Erbe, R.W. Reversion to methionine independence in simian virus 40-transformed human and malignant rat fibroblasts is associated with altered ploidy and altered properties of transformation. Proc. Natl. Acad. Sci. USA **76**, 1313-1317, 1979.
- Coalson, D.W., Mecham, J.O., Stern, P.H., and Hoffman, R.M. Reduced availability of endogenously synthesized methionine for S-adenosylmethionine formation in methionine-dependent cancer cells. Proc. Natl. Acad. Sci. USA **79**, 4248-4251, 1982.
- Stern, P.H., Mecham, J.O., Wallace, C.D. and Hoffman, R.M. Reduced free-methionine in methionine-dependent SV40-transformed human fibroblasts synthesizing apparently normal amounts of methionine. J. Cell. Physiol. **117**, 9-14, 1983.
- Stern, P.H., and Hoffman, R.M. Elevated overall rates of transmethylation in cell lines from diverse human tumors. In Vitro **20**, 663-670, 1984.

5) I pioneered the field of cancer epigenetics:

- Hoffman, R.M. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. A review and synthesis. Biochim. Biophys. Acta **738**, 49-87, 1984.

6) I pioneered the field of methionine-deprivation cancer therapy:

- Stern, P.H. and Hoffman, R.M. Enhanced in vitro selective toxicity of chemotherapeutic agents for human cancer cells based on a metabolic defect. J. Natl. Cancer Inst. **76**, 629-639, 1986
- Sun, X., Yang, Z., Li, S., Tan, Y., Zhang, N., Wang, X., Yagi, S., Yoshioka, T., Takimoto, A., Mitsushima, K., Suginaka, A., Frenkel, E.P., and Hoffman, R.M. *In vivo* efficacy of recombinant methioninase is enhanced by the combination of polyethylene glycol conjugation and pyridoxal 5′ phosphate supplementation. Cancer Research **63,** 8377-8383, 2003.
- Yang, Z., Wang, J., Yoshioka, T., Li, B., Lu, Q., Li, S., Sun, X., Tan, Y., Yagi, S., Frenkel, E.P., and Hoffman, R.M. Pharmacokinetics, methionine depletion, and antigenicity of recombinant methioninase in primates. Clinical Cancer Research **10,** 2131-2138, 2004.
- Yang, Z., Sun, X., Li, S., Tan, Y., Wang, X., Zhang, N., Yagi, S., Takakura, T., Kobayashi, Y., Takimoto, A., Yoshioka, T., Suginaka, A., Frenkel, E.P., and Hoffman, R.M. Circulating half-life of PEGylated recombinant methioninase holoenzyme is highly dose dependent on cofactor pyridoxal-5′-phosphate. Cancer Research **64**, 5775-5778, 2004.

- Yang, Z., Wang, J., Lu, Q., Xu, J., Kobayashi, Y., Takakura, T., Takimoto, A. Yoshioka, T., Lian, C., Chen, C., Zhang, D., Zhang, Y., Li, S., Sun, X., Tan, Y., Yagi, S., Frenkel, E.P., and Hoffman, R.M. PEGylation confers greatly extended half-life and attenuated immunogenicity to recombinant methioninase in primates. Cancer Research **64**, 6673-6678, 2004.

7) I was the first to compare gene expression in normal and cancer cells:

- Williams, J., Hoffman, R.M. and Penman, S. The extensive homology between mRNA sequences of normal and SV40-transformed human fibroblasts. Cell **11**, 901-907, 1977.

8) I pioneered the field of non-viral gene therapy:

- Hoffman, R.M., Margolis, L.B. and Bergelson, L.D. Binding and entrapment of high molecular weight DNA by lecithin liposomes. FEBS Letters **93**, 365-368, 1978.
- Li, L., Hoffman, R.M. The feasibility of targeted selective gene therapy of the hair follicle. Nature Medicine **1**, 705-706, 1995.

9) I developed the first practical *in vitro* drug response assay for human cancer patients to enable individualized cancer therapy:

- Freeman, A.E. and Hoffman, R.M. In vivo-like growth of human tumors in vitro. Proc. Natl. Acad. Sci. USA **83**, 2694-2698, 1986.
- Vescio, R.A., Redfern, C.H., Nelson, T.J., Ugoretz, S. Stern, P.H. and Hoffman, R.M. *In vivo*-like drug responses of human tumors growing in three-dimensional gel-supported, primary culture. Proc. Natl. Acad. Sci. USA **84,** 5029-5033, 1987.
- Furukawa, T., Kubota, T., Hoffman, R.M. Clinical applications of the histoculture drug response assay. Clinical Cancer Research **1**, 305-311, 1995.
- Kubota, T., Sasano, N., Abe, O., Nakao, I., Kawamura, E., Saito, T., Endo, M., Kimura, K., Demura, H., Sasano, H., Nagura, H., Ogawa, N., Hoffman, R.M. Potential of the histoculture drug response assay to contribute to cancer patient survival. Clinical Cancer Research **1**, 1537-1543, 1995.

10) I pioneered the field of culturing hair-growing skin:

- Li, L., Margolis, L.B. and Hoffman, R.M. Skin toxicity determined *in vitro* by three-dimensional, native-state histoculture. Proc. Natl. Acad. Sci. USA **88**, 1908-1912, 1991.
- Li, L., Margolis, L.B., Paus, R. and Hoffman, R.M. Hair shaft elongation, follicle growth, and spontaneous regression in long-term, gelatin sponge-supported histoculture of human scalp skin. Proc. Natl. Acad. Sci. USA **89**, 8764-8768, 1992.

11) I developed the first clinically-relevant mouse models of human cancer:

- Fu, X.Y., Besterman, J.M., Monosov, A. and Hoffman, R.M. Models of human metastatic colon cancer in nude mice orthotopically constructed by using histologically intact pa161ient specimens. Proc. Natl. Acad. Sci. USA **88**, 9345-9349, 1991.
- Fu, X., Guadagni, F. and Hoffman, R.M. A metastatic nude-mouse model of human pancreatic cancer constructed orthotopically from histologically intact patient specimens. Proc. Natl. Acad. Sci. USA **89**, 5645-5649, 1992.

12) I discovered the specific role of the host organ in cancer growth:

- Togo, S., Shimada, H., Kubota, T., Moossa, A.R., Hoffman, R.M. Host organ specifically determines cancer progression. Cancer Res. **55**, 681-684, 1995.

13) I discovered the governing step of metastasis:

- Kuo, T-H., Kubota, T., Watanabe, M., Furukawa, T., Teramoto, T., Ishibiki, K., Kitajima, M., Moossa, A.R., Penman, S., Hoffman, R.M. Liver colonization competence governs colon cancer metastasis. Proc. Natl. Acad. Sci. USA **92**, 12085-12089, 1995.

14) I co-discovered the genetic basis of cell senescence:

- Schmitt, C.A., Fridman, J.S., Yang, M., Baranov, E., Hoffman, R.M. and Lowe, S.W. Dissecting p53 tumor suppressor functions in vivo. Cancer Cell **1**, 289-298, 2002 (Cover story).
- Schmitt, C.A., Fridman, J.S., Yang, M., Lee, S., Baranov, E., Hoffman, R.M., and Lowe, S.W. A senescence program controlled by p53 and $p16^{INK4a}$ contributes to the outcome of cancer therapy. Cell **109**, 335-346, 2002.

15) I pioneered *in vivo* imaging using fluorescent proteins:

- Hoffman, R.M. The multiple uses of fluorescent proteins to visualize cancer *in vivo*. Nature Reviews Cancer **5**, 796-806, 2005.
- Chishima, T., Miyagi, Y., Wang, X., Yamaoka, H., Shimada, H., Moossa, A.R. and Hoffman, R.M. Cancer invasion and micrometastasis visualized in live tissue by green fluorescent protein expression. Cancer Research **57**, 2042-2047, 1997.
- Naumov, G.N., Wilson, S.M., MacDonald, I.C., Schmidt, E.E., Morris, V.L., Groom, A.C., Hoffman, R.M., Chambers, A.F. Cellular expression of green fluorescent protein, coupled with high-resolution *in vivo* videomicroscopy, to monitor steps in tumor metastasis. J. Cell Sci. **112**, 1835-1842, 1999.
- Yang, M., Baranov, E., Jiang, P., Sun, F-X., Li, X-M., Li, L., Hasegawa, S., Bouvet, M., Al-Tuwaijri, M., Chishima, T., Shimada, H., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body optical imaging of green fluorescent protein-expressing tumors and metastases. Proc. Natl. Acad. Sci. USA **97**, 1206-1211, 2000.
- Yang, M., Baranov, E., Moossa, A.R., Penman, S., Hoffman, R.M. Visualizing gene expression by whole-body fluorescence imaging. Proc. Natl. Acad. Sci. USA **97**, 12278-12282, 2000.
- Yang, M., Baranov, E., Li., X-M., Wang, J-W., Jiang, P., Li, L., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body and intravital optical imaging of angiogenesis in orthotopically implanted tumors. Proc. Natl. Acad. Sci. USA **98**, 2616-2621, 2001.
- Zhao, M., Yang, M., Baranov, E., Wang, X., Penman, S., Moossa, A.R., and Hoffman, R.M. Spatial-temporal imaging of bacterial infection and antibiotic response in intact animals. Proc. Natl. Acad. Sci. USA **98**, 9814-9818, 2001.
- Yang, M., Baranov, E., Wang, J-W., Jiang, P., Wang, X., Sun, F-X., Bouvet, M., Moossa, A.R., Penman, S., and Hoffman, R.M. Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model. Proc. Natl. Acad. Sci. USA **99**, 3824-3829, 2002.
- Bouvet, M., Wang, J-W., Nardin, S.R., Nassirpour, R., Yang, M., Baranov, E., Jiang, P., Moossa, A.R., and Hoffman, R.M. Real-time optical imaging of primary tumor growth and multiple metastatic events in a pancreatic cancer orthotopic model. Cancer Research **62**, 1534-1540, 2002 (Cover story).
- Yang, M., Li, L., Jiang, P., Moossa, A.R., Penman, S., and Hoffman, R.M. Dual-color fluorescence imaging distinguishes tumor cells from induced host angiogenic vessels and stromal cells. Proc. Natl. Acad. Sci. USA **100**, 14259-14262, 2003.
- Mitsiades, C.S., Mitsiades, N.S., Bronson, R.T., Chauhan, D., Munshi, N., Treon, S.P., Maxwell, C.A., Pilarski, L., Hideshima, T., Hoffman, R.M., and Anderson, K.C. Fluorescence imaging of multiple myeloma cells in a clinically relevant SCID/NOD *in vivo* model: biologic and clinical implications. Cancer Research **63**, 6689-6696, 2003.
- Yamamoto, N., Jiang, P., Yang, M., Xu, M., Yamauchi, K., Tsuchiya, H., Tomita, K., Wahl, G.M., Moossa, A.R., and Hoffman, R.M. Cellular dynamics visualized in live cells *in vitro* and *in vivo* by differential dual-color nuclear-cytoplasmic fluorescent-protein expression. Cancer Research **64**, 4251-4256, 2004.
- Simberg, D., Duza, T., Park, J.H., Essler, M., Pilch, J., Zhang, L., Derfus, A.M., Yang, M., Hoffman, R.M., Bhatia, S., Sailor, M.J., and Ruoslahti, E. Biomimetic amplification of nanoparticle homing to tumors. Proc. Natl. Acad. Sci. USA **104**, 932-936, 2007.
- Hoffman, R.M., and Yang, M. Color-coded fluorescence imaging of tumor-host interactions. Nature Protocols **1**, 928-935, 2006.
- Hoffman, R.M., and Yang, M. Subcellular imaging in the live mouse. Nature Protocols **1**, 775-782, 2006.
- Hoffman, R.M., and Yang, M. Whole-body imaging with fluorescent proteins. Nature Protocols **1**, 1429-1438, 2006.

16) I was the first to image the tumor microenvironment:

- Yang, M., Jiang, P., and Hoffman, R.M. Whole-body subcellular multicolor imaging of tumor-host interaction and drug response in real time. Cancer Research **67**, 5195-5200, 2007

17) I discovered the only known adult pluripotent stem cells:

- Li, L., Mignone, J., Yang, M., Matic, M., Penman, S., Enikolopov, G., and Hoffman, R.M. Nestin expression in hair follicle sheath progenitor cells. Proc. Natl. Acad. Sci. USA **100**, 9958-9961, 2003.
- Amoh, Y., Li, L., Yang, M., Moossa, A.R., Katsuoka, K., Penman, S., and Hoffman, R.M. Nascent blood vessels in the skin arise from nestin-expressing hair follicle cells. Proc. Natl. Acad. Sci. USA **101**, 13291-13295, 2004.
- Amoh, Y., Li, L., Campillo, R., Kawahara, K., Katsuoka, K., Penman, S., and Hoffman, R.M. Implanted hair follicle stem cells form Schwann cells that support repair of severed peripheral nerves. Proc. Natl. Acad. Sci. USA **102**, 17734-17738, 2005.
- Amoh, Y., Li, L., Katsuoka, K., Penman, S., and Hoffman, R.M. Multipotent nestin-positive, keratin-negative hair-follicle-bulge stem cells can form neurons. Proc. Natl. Acad. Sci. USA **102**, 5530-5534, 2005.

18) I was the first to determine what controlled the clonality of metastasis:

- Yamamoto, N., Yang, M., Jiang, P., Xu, M., Tsuchiya, H., Tomita, K., Moossa, A.R., and Hoffman, R.M. Determination of clonality of metastasis by cell-specific color-coded fluorescent-protein imaging. Cancer Research **63,** 7785-7790, 2003.

19) I discovered the first bacteria that specifically target and can completely eradicate cancer:

- Zhao, M., Yang, M., Li, X-M., Jiang, P., Li, S., Xu, M., and Hoffman, R.M. Tumor-targeting bacterial therapy with amino acid auxotrophs of GFP-expressing *Salmonella typhimurium*. Proc. Natl. Acad. Sci. USA **102**, 755-760, 2005.
- Zhao, M., Yang, M., Ma, H., Li, X., Tan, X., Li, S., Yang, Z., and Hoffman, R.M. Targeted therapy with a *Salmonella typhimurium* leucine-arginine auxotroph cures orthotopic human breast tumors in nude mice. Cancer Research **66**, 7647-7652, 2006.
- Zhao, M., Geller, J., Ma, H., Yang, M., Penman, S., and Hoffman, R.M. Monotherapy with a tumor-targeting mutant of *S. typhimurium* cures orthotopic metastatic mouse models of human prostate cancer. Proc. Natl. Acad. Sci. USA **104**, 10170-10174, 2007.
- Arrach, N., Zhao, M., Porwollik, S., Hoffman, R.M., and McClelland, M. *Salmonella* promoters preferentially activated inside tumors. Cancer Research **68**, 4827-4832, 2008.

20) I discovered that passenger stromal cells are necessary for metastasis:

- Bouvet, M., Tsuji, K., Yang, M., Jiang, P., Moossa, A.R., and Hoffman, R.M. *In vivo* color-coded imaging of the interaction of colon cancer cells and splenocytes in the formation of liver metastases. Cancer Research **66**, 11293-11297, 2006.

21) I discovered the mechanism of chemotherapy-induced alopecia:

- Amoh, Y., Li, L., Moossa, A.R., Katsuoka, K., and Hoffman, R.M. Chemotherapy targets the hair-follicle vascular network but not the stem cells. J. Invest. Dermatol. **127**, 11-15, 2007.

22) I developed the first recombinant enzyme-based diagnostics for homocysteine, vitamin B_6 and cysteine:

- Tan, Y., and Hoffman, R.M. A highly sensitive single-enzyme homocysteine assay. Nature Protocols **3**, 1388-1394, 2008.
- Han, Q., and Hoffman, R.M. Enzymatic assay for total plasma Cys. Nature Protocols **3**, 1778-1781, 2008.
- Han, Q., and Hoffman, R.M. Nonradioactive enzymatic assay for plasma and serum vitamin B_6. Nature Protocols **3**, 1815-1819, 2008.

23) I developed the basis for fluorescence-guided cancer surgery:

- Kishimoto, H., Zhao, M., Hayashi, K., Urata, Y., Tanaka, N., Fujiwara, T., Penman, S., and Hoffman, R.M. In vivo internal tumor illumination by telomerase-dependent adenoviral GFP for precise surgical navigation. Proc. Natl. Acad. Sci. USA **106(34)**, 14514-14517, 2009.
- Green Surgery, Barbara R. Jasny, Editors' Choice. Science **325**, 1321, 11 September 2009.

24) I co-discovered that blood vessels in tumors can be formed from cancer cells:

- Soda, Y., Marumoto, T., Friedmann-Morvinski, D., Soda, M., Liu, F., Michiue, H., Pastorino, S., Yang, M., Hoffman, R.M., Kesari, S., Verma, I.M. Transdifferentiation of glioblastoma cells into vascular endothelial cells. Proc. Natl. Acad. Sci. USA **108**, 4274-4280, 2011 (Cover story).

25) I co-discovered that tumor-infiltrating T-cells stimulate cancer metastasis:

- Tan, W., Zhang, W., Strasner, A., Grivennikov, S., Cheng, J.Q., Hoffman, R.M., and Karin, M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature **470**, 548-553, 2011.

POSTDOCTORAL TRAINING:

Department of Biology Harvard University With the late Professor John R. Raper	1971-1973
Massachusetts General Hospital Harvard Medical School With Dr. Richard W. Erbe and Professor John W. Littlefield	1973-1975
USA-USSR National Academy of Sciences Exchange Fellow The Shemyakin Institute of Bioorganic Chemistry Academy of Sciences, Moscow, USSR With Professor L.D. Bergelson	1976-1977
Weizmann Institute of Science Rehovot, Israel With Dr. Carol Prives	1978

PREVIOUS ACADEMIC POSITIONS:

Instructor of Pediatrics Harvard Medical School Massachusetts General Hospital	1975-1979
Assistant Professor, Department of Pediatrics University of California, San Diego School of Medicine	1979-1983
Associate Professor, Department of Pediatrics University of California, San Diego School of Medicine	1983-1990
Professor, Department of Pediatrics University of California, San Diego School of Medicine	1990-1995

PROFESSIONAL SOCIETIES:

1. Society for *In Vitro* Biology
2. American Association of Cancer Research
3. American Society for Clinical Oncology
4. Society of Surgical Oncology
5. American Society for Cell Biology
6. Metastasis Research Society
7. Japanese Cancer Association
8. Japanese Society of Clinical Oncology (First American Member)
9. Japanese Metastasis Research Society (First American Member)
10. Japanese Society of Human Cell
11. Preclinical Therapeutic Model Group of the European Organization for Research and Treatment of Cancer
12. Chinese Society for Clinical Oncology (First American Member)
13. International Society for Stem Cell Research

BOARDS:

Ad-Hoc Reviewer National Cancer Institute	1986-present

EDITORIAL BOARDS:

Anticancer Research	1985-present
In Vitro Cellular and Developmental Biology	1987-present
Associate Editor, *Clinical Cancer Research*	2000-Present

TEACHING AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO:

Biology 112:	"Cell and Molecular Biology" Spring and Fall With Professor Gordon Sato	1980
Pediatrics 233:	"Genes and Cancer" Winter	1982-1994
Pediatrics 235:	"New Biological Approaches to Cancer Prevention and Treatment" Spring	1983-1994
Pediatrics 237:	"Biochemical Genetics of Aging" Fall	1984-1994

UNIVERSITY COMMITTEES:

Admissions Committee University of California, San Diego School of Medicine	1983-1985
Electives Committee University of California, San Diego School of Medicine	1989-1990

HONORS AND AWARDS:

Hononary Professor Fudan University, Shanghai Medical College Shanghai, China	2010
A.N. Belozersky Medal Moscow State University	1990
Research Career Development Award National Cancer Institute	1982-1987
Fellow of the Leukemia Society of America	1979-1981
Fellow of the Medical Foundation of Boston	1976-1977
United States National Academy of Sciences Exchange Fellowship Shemyakin Institute of Bioorganic Chemistry Moscow, USSR.	1976-1977
Postdoctoral Fellowship Awardee National Institutes of Health	1974, 1976, 1978
National Institutes of Health Postdoctoral Training Grant Fellow Harvard Medical School	1973-1974
Postdoctoral Research Fellow Harvard University	1971-1973
National Institutes of Health Training Grant Predoctoral Fellowship Harvard University	1966-1971
Phi Beta Kappa State University of New York Buffalo, New York	1964

LECTURES AT SCIENTIFIC CONFERENCES:

International Symposium on "The biochemistry of S-adenosylmethionine as a basis of drug design" Bergen, Norway Lecture entitled "Cancer, methionine and transmethylation. "	1985
Federation of American Societies for Experimental Biology Summer Research Conference entitled "Folic acid, B-12, and one-carbon metabolism" Saxtons River, Vermont Lecture entitled "Altered methionine metabolism and transmethylation in human cancer cells."	1986
Gordon Research Conference on Cancer New London, New Hampshire Lecture entitled "Methionine, transmethylation and cancer."	1987

Invited lecturer, Tissue Culture Association Conference 1988
Las Vegas, Nevada
Lecture entitled "Partitioning of methyl groups in cancer and normal cell types."

Federation of American Societies for 1989
Experimental Biology Summer Research Conference
Copper Mountain, Colorado
Lecture entitled "Cancer, methionine metabolism and transmethylation."

Invited Lecturer, Dae Han Biochemical Society 1990
Seoul, Korea
Lecture entitled "Altered methionine metabolism, unbalanced
global cellular transmethylation and cancer."

Invited Lecturer, Korean Association of Molecular Biology 1990
Pusan, Korea
Lecture entitled "Rational evaluation and design of cancer drugs. "

Third International Conference of Anticancer Research 1990
Marathon, Greece
Lecture entitled "The development of clinically relevant *in vitro* and *in vivo*
preclinical models: Three-dimensional gel-supported *in vitro* histoculture and
orthotopic implantation and metastasis of human tumors in nude mice. "

Invited Lecturer, Regina Elena Cancer Center 1991
Rome, Italy
Lecture entitled "Patient-like *in vitro* and *in vivo* pre-clinical models of human cancer."

Gordon Research Conference on Cancer Chemotherapy 1992
New London, New Hampshire
Lecture entitled "Orthotopic-transplantation animal models for the identification
of new anticancer drugs. "

Fourth International Congress of the Metastasis Research Society 1992
Paris, France
Lecture entitled "The nude mouse comes to the cancer clinic:
Metastatic models of the major cancer types constructed by
orthotopic transplantation of histologically-intact patient specimens."

First Congress of the International Society for Experimental Microsurgery 1992
Rome, Italy
Lecture entitled "Microsurgery, orthotopic human tumor transplantation
and the nude mouse: Patent-like metastatic models of human cancer. "

Keystone Symposium on Discovery and Development of Therapeutic Compounds 1993
Snowmass, Colorado
Session Chairman, Lecture entitled "Orthotopic models for treatment
evaluation *in vivo* using histologically-intact cancer patient specimens."

FASEB Summer Conference 1993
Copper Mountain, Colorado
Lecture entitled "MetaMouse®: the nude mouse comes to the cancer clinic
via orthotopic transplantation of architecturally-intact patient tumors. "

Hellenic Society for Breast Cancer Research, First International Congress 1993
Corfu, Greece
Lecture entitled "Patient-like cancer models and therapeutics specific for cancer- an approach to the next generation of treatment"

FASEB Summer Conference 1994
Copper Mountain, Colorado
Lecture entitled "Tissue architecture and metastases"

Japan Society of Human Cell Meeting 1995
Toyoma City, Japan
Lecture entitled "*In vitro* drug response assays are clinically useful in cancer"

Hellenic Society For Breast Cancer Research, Second International Congress 1995
Kos Island, Greece
Lecture entitled "Methioninase (AC9301): A selective antitumor agent with a new mechanism of action."

6th International Congress on Anticancer Treatments 1996
Paris, France
Lecture entitled "Pilot phase I clinical trial of methioninase: serum depletion of methionine without acute toxicity."

6th International Congress on Anticancer Treatments 1996
Paris, France
Lecture entitled "The gelatinase-A Inhibitor CT1746 arrests human colon tumor growth and spread and increases survival in a patient like orthotopic model in nude mice."

IBC USA Alopecia Conference 1996
San Diego, California
Lecture entitled "The feasibility of targeted selective gene therapy of the hair follicle."

Shanghai International Symposium on Liver Cancer & Hepatitis 1996
Shanghai, China
Lecture entitled "Liver colonization capability governs metastatic potential"

Cambridge Healthtech Institute's Engineered Animal Models 1996
Baltimore, Maryland
Lecture entitled "MetaMouse® Models of Cancer: Clinically Relevant Orthotopic Models of Cancer Growth and Metastasis"

Third International Conference of the Asian Clinical Oncology Society (ACOS) 1996
Kunming, China
Lecture entitled "Taking chemotherapy from random to rational with the histoculture drug response assay"

The International Congress on Human Cell and Cell Culture 1996
Tokyo, Japan
Lecture entitled "Nutritional regulation of cancer growth by use of methioninase: possible apoptotic cell kill mechanism"

The Sixth International Congress of the Metastasis Research Society 1996
Gent, Belgium
Lecture entitled "Surgical Orthotopic Implantation (SOI): A new approach to develop clinically-relevant models of human metastatic cancer in immunodeficient rodents"

IBC's Alopecia Conference 1996
Washington, D.C.
Lecture entitled "Hair Follicle Targeting of Large and Small Molecules with Topical Liposomes"

First Panhellenic Congress of Tumors Markers with International Participation 1996
Athens, Greece
Lecture entitled "Methionine dependence as a Possible Universal Therapeutic Tumor Marker"

Seventh International Congress on Anticancer Treatment (SOMPS) 1997
Paris, France
Lecture entitled "R-Methioninase as a potential universal apoptotic antitumor agent"

Seventh International Congress on Anticancer Treatment (SOMPS) 1997
Paris, France
Lecture entitled "Acquisition of broad range multidrug resistance in recurrent breast cancer"

IBC's Drug Discovery Approaches to Cosmeceuticals Conference 1997
East Rutherford, NJ
Lecture entitled "Hair producing histoculture skin for the discovery of a new generation of hair follicle targeted cosmeceuticals and therapeutics

30th Annual Meeting of the Japanese Research Society for Appropriate Cancer Chemotherapy 1997
Tokyo, Japan
Lecture entitled "Histoculture Drug Response Assay"

IBC's Delivery Technologies for Cosmetic Ingredients Conference 1997
Philadelphia, PA
Lecture entitled "Cosmetic and therapeutic molecules targeted to hair follicles by topical liposomal application"

6th Hellenic Congress on Senology and the 3rd International Congress of the Hellenic Society for Breast Cancer Research 1997
Alexandroupolis, Greece
Lecture entitled "Cachexia in breast cancer and elevated amino-acid requirements of tumors: Selective biological targets for therapy"

FASEB Summer Research Conference on Biological Methylation 1997
Saxtons River, Vermont
Lecture entitled "Alterations in methionine dependence and transmethylation in cancer: methioninase for therapy"

3rd International Symposium on Polymer Therapeutics 1998
London, England
Lecture entitled "Polyethylene glycol conjugation of recombinant methioninase for cancer therapy"

8th International Congress on Anti-Cancer Treatment 1998
Paris, France
Lecture entitled "Polyethylene glycol conjugation of recombinant methioninase for cancer therapy"

Gordon Research Conference on Lasers in Medicine and Biology — 1998
Meriden, New Hampshire
Lecture entitled "Green fluorescent protein: A new light to study metastatsis and angiogenesis"

25th Balken Medical Week Conference — 1998
Ioannina, Greece
Lecture entitled "Methioninase: A new selective cancer therapy"

7th Annual Meeting of the Japanese Association for Metastasis Research — 1998
Sapporo, Japan
Lecture entitled "Green fluorescent protein: A new light to study the role of angiogenesis in metastasis"

SPIE's International Symposium on Biomedical Optics — 1999
San Jose, CA
Lecture entitled "Green fluorescent protein: A new light to visualize metastasis and angiogenesis in cancer"

2nd International Symposium on GFP – The Green Fluorescent Protein — 1999
San Diego, CA
Lecture entitled "Fluorescent optical tumor imaging (FOTI) of human cancers in live nude mice"

4th International Conference of the Asian Clinical Oncology Society (ACOS) — 1999
Bali, Indonesia
Lecture entitled "Individualizing cancer chemotherapy by tumor histoculture"

58th Annual Meeting of the Japanese Cancer Association — 1999
Hiroshima, Japan
Lecture entitled "Orthotopic transplant mouse models with green fluorescent protein-expressing cancer cells to visualize micrometastasis and angiogenesis"

SPIE's International Symposium on Biomedical Optics — 2000
San Jose, CA
Lecture entitled "External optical imaging of green fluorescent protein-expressing metastatic tumors"

VIII International Congress of the Metastasis Research Society — 2000
London, UK
Lecture entitled "GFP tumor, metastases, and angiogenesis whole-body imaging"

9th Shizuoka Drug Delivery Conference — 2000
Shizuoka, Japan
Lecture entitled "Polyethylene glycol conjugation of recombinant methioninase for cancer therapy"

World Congress on In Vitro Biology — 2000
San Diego, California
Lecture entitled "Individualized cancer chemotherapy by tumor histoculture"

13th International Congress on Photobiology — 2000
San Francisco, California
Lecture entitled "*In vivo* high-throughput drug screen with whole-body imaging GFP tumor models"

11th International Symposium for Bioluminescence and Chemiluminescence — 2000
Monterey, California
Lecture entitled "Whole-body optical imaging of green fluorescent protein-expressing tumors"

3rd International Symposium on Minimal Residual Cancer — 2001
Hamburg, Germany
Lecture entitled "Mouse Models: Whole-body and intra-vital fluorescence imaging of minimal residual disease, tumor growth and progression"

54th Annual Cancer Symposium of the Society of Surgical Oncology — 2001
Washington, DC
Lecture entitled "Visualizing gene expression by whole-body fluorescence imaging"

Asan Medical Center, Dept. of General Surgery and Div. Of Hematology/Oncol. — 2001
Seoul, Korea
Special Lecture entitled "The clinical significance of Histoculture Drug Response Assay (HDRA) in solid tumors"

92nd Annual American Association for Cancer Research Annual Meeting — 2001
Educational Session 7 – Approaches in Drug Development and Toxicology
New Orleans, Louisiana
Lecture entitled "Whole-body fluorescence imaging of GFP of tumor growth, Metastasis, angiogenesis and gene expression"

NCI Mouse Models of Human Cancers Consortium Preclinical Trials Meeting — 2001
Bethesda, MD
Lecture entitled "*In vivo* imaging"

NIH Mouse Models of Mammary Cancer Consortium Meeting — 2001
Bethesda, MD
Lecture entitled "Whole-body fluorescence imaging with GFP of tumor growth, metastasis, angiogenesis and gene expression"

62nd Annual Meeting of the Society of Investigative Dermatology — 2001
Washington, DC
Oral Presentation "Gene therapy of growing hair shafts"

NCI Mouse Models of Human Cancers Consortium Lung Cancer Workshop — 2001
Boston, MA
Lecture entitled "GFP imaging of lung tumors in nude mice"

29th Annual Meeting of the American Society for Photobiology — 2001
Chicago, IL
Lecture entitled "Real-time whole-body fluorescence imaging of bacterial infection"

NCI Preclinical Angiogenesis Imaging Models Working Group Meeting — 2001
Washington, DC
Lecture entitled "GFP imaging of angiogenesis in mice"

IIR's 3rd Annual Conference on Angiogenesis: Innovative Science and — 2001
New Applications
Boston, MA
Lecture entitled" Whole-body and intravital optical imaging of angiogenesis in orthotopically implanted tumors"

2nd Annual Molecular Imaging Workshop — 2001
East Lansing, MI
Lecture entitled "Whole-body fluorescence imaging with GFP of tumor growth, metastasis, angiogenesis and gene expression"

15th Annual BACT Symposium — 2001
Nagoya, Japan
Lecture entitled "*In vitro* chemosensitivity as a predictor of outcome in patients with head and neck cancer"

University of Texas NSF IGERT Program Seminar — 2001
Austin, TX
Lecture entitled "Whole-body imaging of tumors, metastasis, micrometastasis, angiogenesis and gene expression"

Massachusetts General Hospital, Wellman Laboratories of Photomedicine Lecture Series — 2002
Boston, MA
Lecture entitled "Optical imaging with GFP"

Sidney Kimmel Cancer Center Seminar Series — 2002
San Diego, CA
Lecture entitled "Optical imaging with GFP"

SPIE's BIOS 2002 Symposium – Conference on Functional Imaging and Optical Manipulation of Living Cells and Tissues — 2002
San Jose, CA
Lecture entitled "Fluorescence imaging of angiogenesis in green fluorescent protein-transduced tumors"

European School of Haematology's Animal Models of Human Disease: Modeling Human Cancers in the Mouse: A Practical Issue — 2002
Paris, France
Lecture entitled "Whole-body fluorescence imaging of tumor growth, micrometastasis, metastasis, angiogenesis and gene expression"

Showa University, Northern Yokohama Hospital — 2002
Yokohama, Japan
Lecture entitled "Green fluorescent protein imaging of cancer"

UCLA Crump/General Electric/LSI Molecular Imaging Seminar Series — 2002
Los Angeles, CA
Lecture entitled "Optical imaging with GFP"

93rd Annual Meeting of the American Association for Cancer Research — 2002
San Francisco, CA
Lecture entitled "Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model"

University of Texas of M.D. Anderson Cancer Center – Dept. of Cancer Biology's Cancer Metastasis Research Program Seminar Series — 2002
Houston, TX
Lecture entitled "Optical imaging with GFP"

Netherlands Cancer Institute Symposium: In the Footsteps of Antoni Van Leeuwenhoek — 2002
Amsterdam, Netherlands
Lecture entitled "Non-invasive visualization of fluorescent tumors in intact animals"

6th Joint Meeting of the Japan Society of Histochemistry and Cytochemistry and the Histochemical Society — 2002
Seattle, WA
Lecture entitled "Non-invasive visualization of fluorescent tumors in intact animals"

9th Annual Meeting of the European Hair Research Society — 2002
Brussels, Belgium
Lecture entitled "Selective hair follicle targeting"

6th Congress of the International Society for Experimental Microsurgery — 2002
San Diego, CA
Lecture entitled "Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model"

1st Annual Meeting of the Society of Molecular Imaging — 2002
Boston, MA
Lecture entitled "Multi-color imaging with fluorescent proteins"

9th International Congress of the Metastasis Research Society — 2002
Chicago, IL
Lecture entitled "Dual-color imaging of tumors and metastasis in mice"

2nd Petersberg Euroconference — 2002
Petersberg, Germany
Lecture entitled "*In vivo* fluorescence resonance energy transfer (FRET) measurement"

Jichi Medical School — 2002
Jichi, Japan
Lecture entitled "Green fluorescent protein imaging of tumor cells *in vivo*"

Dana-Farber/Harvard Cancer Center Cancer Cell Biology Program's Minisymposium on Molecular Imaging — 2002
Boston, MA
Lecture entitled "Dual-color *in vivo* imaging of cancer"

The Hebrew University of Jerusalem — 2003
Jerusalem, Israel
Lecture entitled "A hair-brain connection: Nestin expressing hair follicle stem cells"

The Hebrew University of Jerusalem — 2003
Jerusalem, Israel
Lecture entitled "Whole-body optical imaging of tumor growth, metastasis and host reaction"

Russian Academy of Sciences, Institute of Gene Biology — 2003
Moscow, Russia
Lecture entitled "*In vivo* molecular imaging with fluorescent protein"

M.D. Anderson Cancer Center 2003
1st Course of Molecular Mechanisms in Brain Tumors
Montgomery, TX
Lecture entitled "Use of green fluorescent protein and red fluorescent protein to follow brain tumors and their therapy *in vivo* by whole-body imaging"

National Institute of Infectious Diseases 2003
Symposia on Bioimaging and Nano-technology
Tokyo, Japan
Lecture entitled "Imaging analysis of angiogenesis and metastasis of cancer"

Roswell Park Cancer Institute 2003
Molecular and Cellular Biophysics Department Special Seminar
Buffalo, NY
Lecture entitled "Multi-colored imaging of multiple events in tumor progression"

76th Annual Meeting of the Japanese Orthopaedic Association 2003
Kanazawa, Japan
1) Lecture entitled "Correlation of green fluorescent protein with standard x-ray in assessing prostate cancer bone lesions in nude mice"
2) Lecture entitled "Multicolor in vivo cellular and molecular imaging with GFP and RFP"

15th Annual Pezcoller Symposium (see *Cancer Research* **64**, 2929-2933, 2004) 2003
Rovereto, Italy
Lecture entitled "Real-time visualization of cancer cellular and molecular biology in the intact animal"

Tumor Biology Center at the University of Freiburg's Symposium on Novel Approaches 2003
for the Discovery of Anticancer Agents.
Freiburg, Germany
Lecture entitled "Imaging tumor progression *in vivo*"

Dedication of Dong Fang Hospice in honor of founder Professor Jia Xi Li and in memory 2003
Of former Minister of Health Minzhang Chen
Beijing, P.R. China
Lecture entitled "Drug evaluation in pancreatic cancer MetaMouse"

4th International Symposium on Minimal Residual Cancer 2003
Oslo, Norway
Lecture entitled "Visualizing live tumor cells interacting with host cells color-Coded with green fluorescent protein and red fluorescent protein"

SPIE's BIOS 2004 Symposium – Genetically engineered and optical probes 2004
for biomedical applications II: Genetically engineered fluorescent proteins and bioluminescent probes.
San Jose, CA
Lecture entitled "Dual-color imaging of tumor host interaction with GFP and RFP"

26th Annual University of California of San Diego Assembly in Surgery 2004
San Diego, CA
Lecture entitled "Dual-color fluorescence imaging of tumor-host interaction with green and red fluorescent proteins"

Pfizer and Howard Hughes Medical Institute Seminar Series at Connecticut College 2004
New London, CT
Lecture entitled "Multi-color *in vivo* imaging: The new cell biology"

95th American Association for Cancer Research Annual Meeting – 2004
"Meet-the-Expert" Sunrise Session
Orlando, FL
Lecture entitled "Imaging of animal models with GFP"

Kyoto University Graduate School of Medicine, Department of Pharmacology 2004
Kyoto, Japan
Lecture entitled "*In vivo* imaging with fluorescent proteins"

13th Annual Meeting of the Japanese Association for Metastasis Research 2004
Tokyo, Japan
Lecture entitled "*In vivo* imaging with fluorescent proteins"

Mouse Workshop at Murinus GmbH 2004
Hamburg, Germany
Lecture entitled "Multi-color fluorescence imaging *in vivo*: The new cell biology"

4th Intercontinental Meeting of the Hair Research Societies 2004
Berlin, Germany
Lecture entitled "Potential of nestin-expressing hair-follicle stem cells to form neurons and blood vessels"

32nd Annual Meeting of the American Society for Photobiology 2004
Seattle, WA
Lecture entitled "Multi-color *in vivo* imaging with fluorescent proteins"

12th International Congress of the Histochemisty and Cytochemistry 2004
San Diego, CA
Lecture entitled "Rainbow imaging *in vivo*"

University of Washington's Friday Harbor Laboratories Centennial Celebration - 2004
Calcium-Regulated Photoproteins and Green Fluorescent Proteins
Friday Harbor, WA
Lecture entitled "Imaging cell biology *in vivo* with fluorescent proteins"

42nd Annual Meeting of the Japan Society of Clinical Oncology 2004
Kyoto, Japan
Lecture entitled "Multicolor imaging of tumor growth, metastasis and angiogenesis *in vivo*"

19th Annual Meeting of the International Society for Biological Therapy of Cancer 2004
Primer on Biological Therapy of Cancer
San Francisco, CA
Lecture entitled "Rainbow imaging: Cell biology *in vivo*"

Florescent Proteins in Drug Development 2004
In Vivo Molecular Imaging
Cambridge Healthtech Institute
La Jolla, California
Lecture entitled "*In Vivo* imaging with green fluorescent proteins"

19th World Congress of International Society for Digestive Surgery 2004
Yokohama, Japan
Lecture entitled: "*In Vivo* imaging with fluorescent proteins: the new cell biology"

European Molecular Biology Organizations' Course on Light Microscopy 2005
Life Specimens in collaboration with the National University of Singapore,
the Institute of Molecular Cell Biology, and the Institute of Bio and Nanotechnology
Singapore
Lecture entitled "*In vivo* imaging with fluorescent proteins: the new cell biology"

SPIE's BIOS 2005 Symposium – Genetically engineered and optical probes 2005
for biomedical applications III.
San Jose, CA
Lecture entitled "*In vivo* imaging with fluorescent proteins: the new cell biology"

Biophysical Society 49th Annual Meeting 2005
Long Beach, CA
Lecture entitled "Imaging with fluorescent proteins in vivo, the new cell biology"

University of Texas NSF IGERT Program Seminar 2005
Austin, TX
Lecture entitled "*In vivo* imaging with multi-color fluorescent proteins: The new cell biology"

4th Conference on Hyperhomocysteinemia 2005
Saarbrucken, Germany
Lecture entitled "Use of methionine-homocysteine, α, γ-lyases to develop an *in vitro*
Enzymatic diagnostics panel for homocysteine, cysteine, methionine and vitamin B_6."

Joint Congress of the Histochemical Society and the Society for Histochemistry 2005
Noordwijkerhout, The Netherlands
Lecture entitled "Multi-color imaging of the multiple events of tumor progression in
real-time"

66th Annual Meeting of the Society of Investigative Dermatology 2005
St. Louis, MO
Lecture entitled "Nestin-positive, keratin-15-negative primitive stem cells in the hair
follicle capable of forming multiple types of non-hair-follicle cells"

14th Annual Meeting of the Japanese Association for Metastasis Research 2005
Osaka, Japan
Lecture entitled "Multi-color imaging of the multiple events of tumor progression in real-time"

University of Texas, MD Anderson Cancer, Science Park-Research Division, 2005
Virginia Harris Cockrell Cancer Research Institute
Lecture entitled "Multi-color imaging of the multiple events of tumor progression in real time"

1st International Tübingen-Symposium on Pediatric Solid Tumors 2005
Tübingen, Germany
Lecture entitled "Dual-color labeling and fluorescent imaging for in vivo visualization of cytoplasmic and nuclear dynamics of cancer cell migration"

63rd Annual Meeting of the Microscopy Society of America- 2005
Microscopy and Microanalysis 2005
Honolulu, HI
Lecture entitled "Multi-color in vivo imaging with fluorescent proteins: The new cell biology"

10th Anniversary Drug Discovery Technology and Development Conference 2005
Boston, MA
Lecture entitled "In vivo imaging of tissues, cells, organelles, trafficking and gene expression
with multicolor fluorescent proteins in real-time"

Stem Cell Research: A Technology with the Promise to Contribute to All of Medicine 2005
Cambridge Healthtech Institute
Lecture entitled "Hair follicle nestin-expressing stem cells can form neurons"

5th International Symposium on Minimal Residual Cancer 2005
San Francisco, CA
Lecture entitled "Multi-color subcellular imaging of cancer cell dynamics in live animals"

43rd Annual Meeting of the Japan Society of Clinical Oncology 2005
Sapporo, Japan
Lecture entitled "Visualizing the *in vivo* cell biology of metastasis in real time"

35th Annual European Society for Dermatological Research 2005
Tübingen, Germany
Lecture entitled "Multi-potent nestin-positive keratin-negative hair-follicle bulge stem cells can form neurons"

Eisai Oncology Area Committee Meeting 2005
Boston, MA
Lecture entitled "Orthotopic transplantation models and GFP imaging"

13th Annual Meeting of the Society for Hair Science Research 2005
Tokyo, Japan
Lecture entitled "Implanted hair follicle stem cells form Schwann cells which support repair of severed nerves and spinal cord"

SPIE's BIOS 2006 Symposium – Genetically engineered and optical probes 2006
for biomedical applications.
San Jose, CA
Lecture entitled "Multi-color imaging with fluorescent proteins in mice"

Cambridge Healthtech Institute's 13th International Molecular Medicine Tri-Conference 2006
San Francisco, CA
Lecture entitled "Orthotopic Metastatic Mouse Models: the Bridge Linking Preclinical and Clinical Development"

9th Annual Meeting of the American Society for Gene Therapy 2006
Baltimore, MD
Lecture entitled "Metastatic disease in cancer"

47th Annual Meeting of the Japanese Society of Clinical Cytology 2006
Yokohama, Japan
Lecture entitled "Real time multi-color subcellular imaging in mice"

Genomics and Cancer 2006 – German Cancer Research Center (DKFZ) 2006
Heidelberg, Germany
Lecture entitled "*Salmonella typhimurium* amino acid auxotrophs selectively target metastatic prostate and breast tumors"

FEBS Advanced Course: From Functional Genomics to Molecular Proteomics 2006
Yerevan, Armenia
Lecture entitled "Tri-color whole-body cellular imaging of tumor-stroma interaction and drug response in live mice"

21st Century COE Colloquium: Animal Models of Cancer Research – Kyoto University 2006
Kyoto, Japan
Lecture entitled "Development of the new field of in vivo cell biology with multi-color fluorescent proteins"

Dynamic Microscopy 2006 2006
Würzburg, Germany
Lecture entitled "Whole-body subcellular imaging in the live animals"

18th Annual Meeting of the Korean Society for Molecular and Cellular Biology 2006
Seoul, Korea
Lecture entitled "Subcellular imaging in living mice: The new cell biology"

2006 Hwasun Optical Imaging Workshop & Symposium 2006
Seoul, Korea
Lecture entitled "Targeted therapy with a *Salmonella typhimurium* Leucine-Arginine auxotroph cures orthotopic human breast tumors in nude mice"

14th Symposium on Bioluminescence and Chemiluminescence 2006
San Diego, CA
Lecture entitled "Subcellular imaging in vivo: The new cell biology"

Cambridge Healthtech Institute's 3rd Annual Fluorescent Proteins in Drug Development 2006
La Jolla, California
Lecture entitled "Whole-body subcellular imaging in the live mouse"

International Symposia for Bioimaging 2006
Kyoto, Japan
Lecture entitled "Subcellular imaging in vivo: The new cell biology"

Joint Meeting of the 3rd ISC International Conference on Cancer Therapeutics and the 2006
11th International Symposium on Cancer Chemotherapy
Tokyo, Japan
Lecture entitled "The use of fluorescent proteins imaging to visualize new cellular and subcellular targets for cancer chemotherapy in vivo"

SPIE's BIOS 2007 Symposium – Genetically engineered and optical probes 2007
for biomedical applications.
San Jose, CA
Lecture entitled "Tri-color whole-body cellular imaging of tumor-stroma interaction and drug response in live mice"

Keystone Symposium on Imaging Immune Response 2007
Keystone, CO
Lecture entitled "Tri-color imaging of interaction of the host immune system and tumor Cells in the living mouse"

79th Japanese Gastric Cancer Meeting 2007
Nagoya, Japan
Lecture entitled "The use of fluorescent protein imaging to visualize new cellular and subcellular targets for cancer chemotherapy in vivo"

3rd International Conference on Stem Cell Research and Therapeutics 2007
San Diego, CA
Lecture entitled "Multipotency of Hair Follicle Stem Cells to Form Neural Cells

143rd Meeting of the Japanese Society of Veterinary Medicine 2007
Tsukuba City, Japan
Lecture entitled "Subcellular imaging *in vivo*: The new cell biology"

Annual Meeting of the American Society for Investigative Pathology at 2007
Experimental Biology 2007
Washington, DC
Lecture entitled "Whole-body subcellular multicolor imaging of tumor-host interaction and drug response in real time"

54th Annual Meeting of the Japanese Meeting of Animal Science 2007
Tokyo, Japan
Lecture entitled "Whole-body subcellular multicolor imaging of tumor-host interaction and drug response in real time"

2007 University of Pennsylvania's In Vivo Optical Imaging Retreat Progress & 2007
Clinical Translation
Philadelphia, PA
Lecture entitled "Multicolor macro and cellular imaging in vivo"

16th Annual Meeting of the Japanese Metastasis Society 2007
Toyama City, Japan
Lecture entitled "Non-invasive multi-color imaging of cancer and stromal cells in live mice"

Topical Problems of Biophotonics 2007
Nizhny Novgorod, Russia
Lecture entitled "Multicolor whole-body cellular imaging with fluorescent proteins"

Cedars-Sinai Medical Center, Dept. of Surgery and Minimally Invasive Surgical 2007
Technologies Institute, Research Seminar
Los Angeles, CA
Lecture entitled "The pluripotency and clinical potential for regenerative medicine of hair follicle stem cells"

23rd Japan Human Science Bio-Seminar 2007
Tokyo, Japan
Lecture entitled "In vivo molecular imaging with fluorescent proteins: a new paradigm for drug discovery"

4th Symposium in Stem Cell Repair and Regeneration 2007
London, England
Lecture entitled "Multipotency of hair follicle stem cells to form neural cells"

66th Annual Meeting of the Japanese Cancer Association 2007
Yokohama, Japan
Lecture entitled "Direct targeting of lymph node metastasis with a tumor-selective strain of *Salmonella typhimurium*"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on 2008
Genetically Engineered Probes.
San Jose, CA
Lecture entitled "Direct tareting of lymph node metastasis of pancreatic cancer with a tumor-Selective strain of *Salmonella typhimurium*"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on Genetically Engineered Probes. 2008
San Jose, CA
Lecture entitled "Use of GFP for in vivo imaging: Concepts and miconceptions"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on Genetically Engineered Probes. 2008
San Jose, CA
Lecture entitled "Use of telomerase-specific replication-competent adenovirus expressing GFP (OBP-401) to label tumor cells in vivo for surgical navigation"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on Genetically Engineered Probes. 2008
San Jose, CA
Lecture entitled "Imaging enhancement of malignancy by cyclophosphamide: Surprising chemotherapy opposite effects"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on Genetically Engineered Probes. 2008
San Jose, CA
Lecture entitled "Non-invasive in vivo subcellular multicolor imaging of the tumor microenvironment and drug response in real time"

SPIE's BIOS 2008 Symposium – Small Animal Whole-Body Optical Imaging Based on Genetically Engineered Probes. 2008
San Jose, CA
Lecture entitled "Multicolor imaging of intra-lymphatic pancreatic-cancer-cell trafficking using red fluorescent protein-labeled cancer cells and green fluorescent protein monoclonal anti-LYVE-1 antibody"

University of British Columbia Life Science Institute Seminar Series 2008
Vancourver, BC, Canada
Lecture entitled "In vivo molecular imaging with fluorescent proteins: A new paradigm for drug discovery"

31st Postgraduate Assembly in Surgery Conference 2008
San Diego, CA
Marshall J. Orloff Lecture entitled "Animal models of human cancer: What have we learned?

Ordway Research Institute Seminar Series 2008
Albany, NY
Lecture entitled "Color-coded in vivo imaging with fluorescent proteins"

Roswell Park Cancer Institute Pharmacology and Therapeutics Seminar Series 2008
Buffalo, NY
Lecture entitled "Imaging small animals with fluorescent proteins. The new science of in vivo cell biology"

Korean Society for Molecular Imaging Annual Meeting 2008
Seoul, Korea
Lecture entitle "Imaging with fluorescent proteins: The new science of in vivo cell biology"

3rd Meeting of the Japanese Society of Molecular Imaging 2008
Omiya City, Japan
Lecture entitled "Subcellular in vivo imaging: The new cell biology"

3rd Goettingen Meeting on Molecualar and Optical Imaging 2008
Bad Sooden-Allendorf, Germany
Lecture entitled "Imaging with fluorescent proteins: The new science of in vivo cell biology"

25th Conference of the European Society for Microcirculation 2008
Budapest, Hungary
Lecture entitled "Dynamic imaging of cancer cells in the microcirculation"

25th Conference of the European Society for Microcirculation 2008
Budapest, Hungary
Lecture entitled "Measurement of homocysteine microsamples"

1st Advanced Bio-Imaging Workshop at Hawksbury, University of Western Sydney 2008
Hawksbury, Australia
Lecture entitled "Fluorescent proteins for in vivo imaging of cancer and for anticancer drug discovery"

1st Advanced Bio-Imaging Workshop at Hawksbury, University of Western Sydney 2008
Hawksbury, Australia
Lecture entitled "Effective cancer treatment using tumor targeting bacteria"

1st Advanced Bio-Imaging Workshop at Hawksbury, University of Western Sydney 2008
Hawksbury, Australia
Lecture entitled "Subcellular imaging techniques to study tumor-host interactions"

BIO Japan 2008 2008
Yokohama, Japan
Lecture entitled "The use of fluorescent proteins for high resolution multiparameter in vivo imaging"

17th Annual Meeting of the Bioimaging Society (Presidential Symposium) 2008
Chiba, Japan
Lecture entitled "Cellular and subcellular imaging with fluorescent proteins in live mice"

UCSD Moores Cancer Center-Cancer Therapeutics Training Program Lecture Series 2008
La Jolla, CA
Lecture entitled "The multiple uses of fluorescent proteins to visualize cancer in vivo"

SPIE's BIOS 2009 Symposium – Fluorescence In Vivo Imaging Based on Genetically-Engineered 2009
Probes: From Living Cells to Whole Body Imaging IV
San Jose, CA
Lecture entitled "Real-time color-coded cellular imaging of interaction between lung metastasis and splenocytes"

SPIE's BIOS 2009 Symposium – Fluorescence In Vivo Imaging Based on Genetically-Engineered 2009
Probes: From Living Cells to Whole Body Imaging IV
San Jose, CA
Lecture entitled "Selective GFP labeling of cancer metastasis in nude mice by the telomerase-specific replication-competent adenovirus expressinog GFP (OBP-401)"

GTCbio's 5th Stem Cell Research and Therapeutics Conference 2009
Cambridge, MA
Lecture entitled "The pluripotency of hair follicle stem cells to form neurons and other cell types for regenerative medicine"

2nd Pan Pacific Symposium on Stem Cells Research 2009
Taichung, Taiwan
Lecture entitled "The *In Vivo* Revolution: The Use of Fluorescent Proteins to Image Cancer and Other Diseases in Mice"

2nd Pan Pacific Symposium on Stem Cells Research 2009
Taichung, Taiwan
Lecture entitled "The Pluripotency of Hair Follicle Stem Cells and Their Potential Use in Regenerative Medicine"

Japanese Molecular Imaging Meeting 2009
Tokyo, Japan
Lecture entitled "Imaging with Fluorescent Proteins *In Vivo*: The New Revolution"

ChineseAcademy of Medical Sciences and the Peking Union Medical College 2009
Beijing, China
Lecture entitled "The Multiple Uses of Fluorescent Proteins to Visualize Cancer *In Vivo*"

The Hebrew University of Jerusalem – Immunology Seminar 2009
Jerusalem, Israel
Lecture entitled "Imaging with fluorescent proteins – The In Vivo Revolution"

II International Symposium - Topical Problems of Biophotonics 2009
Nizhny Novgorod, Russia
Lecture entitled "Current Technology for *In Vivo* Imaging Using Fluorescent Proteins"

36th Congress of the International Union of Physiological Sciences 2009
Kyoto, Japan
Lecture entitled "Advantages of Hair Follicle Pluripotent Stem (hfPS) Cells over ES and IPS Cells for Regenerative Medicine"

KEIO-LUND (Keio University) Summer School 2009
Tokyo, Japan
Lecture entitled "Advantages of Hair Follicle Pluripotent Stem (hfPS) Cells over ES and IPS Cells for Regenerative Medicine"

Bio Japan 2009 - World Business Forum 2009
Yokohama, Japan
Lecture entitled "Whole-Body Subcellular Multicolor Imaging of Tumor-Host Interaction and Drug Response in Real Time"

WE-Heraeus-Seminar on Molecular Imaging 2009
Bad Honnef, Germany
Lecture entitled "*In Vivo* Imaging with Fluorescent Proteins from Macro to Subcellular"

3rd Advances in Stem Cell Discovery & Development 2009
San Diego, CA
Lecture entitled "Human hair follicle pluripotent stem (hfPS) cells promote regeneration of peripheral-nerve injury: An advantageous alternative to ES and iPS cells"

The 4th International Forum on Laboratory Animal Sci-Tech and The 7th Annual Conference on Laboratory Animal Sci-Tech of North China 2009
Beijing, China
Lecture entitled "*In Vivo* Imaging with Fluorescent Proteins from Macro to Subcellular"

Medical Materials in Taiwan Forum 2009
Kaoshiung, Taiwan
Lecture entitled "*In Vivo* Imaging with Fluorescent Proteins from Macro to Subcellular"

Medical Materials in Taiwan Forum 2009
Kaoshiung, Taiwan
Lecture entitled "The Successful Story of AntiCancer Inc."

National Animal Laboratory Center — 2009
Taipei, Taiwan
Lecture entitled "The *In Vivo* Revolution: The Use of Fluorescent Proteins to Image Cancer and Other Diseases in Mouse Models in Real Time"

35th Annual Meeting of the Taiwanese Dermatological Association — 2009
Kaohsiung, Taiwan
Lecture entitled "Human Hair Follicle Pluripotent Stem (hfPS) Cells for Regenerative Medicine: An Advantageous Alternative to ES and iPS Cells"

Kyushu University (Department of Dermatology) — 2009
Fukuoka, Japan
Lecture entitled "Human Hair Follicle Pluripotent Stem (hfPS) Cells for Regenerative Medicine: An Advantageous Alternative to ES and iPS Cells"

UVP Bio-Imaging International Sales Meeting — 2010
Bangkok, Thailand
Lecture entitled "Fluorescent protein in vivo imaging"

DFG-Excellence Academy of Molecular Imaging — 2010
Aachen, Germany
Lecture entitled "In vivo imaging with fluorescent proteins from macro to subcellular"

6th Annual Stem Cell Research and Therapeutics Conference — 2010
Boston, MA
Lecture entitled "Direct transplantation of uncultured hair follicle pluripotent stem (hfPS) cells promotes the recovery of pheripheral nerve"

9th International Conference of the Asian Clinical Oncology Society — 2011
Gifu, Japan
Lecture entitled "The multiple uses of fluorescent proteins to visualize cancer in vivo"

Japanese National Cancer Center Research Institute — 2011
Tokyo, Japan
Lecture entitled "The GFP revolution in vivo"

Bio-Japan — 2010
Yokohama, Japan
Lecture entitled "The multiple uses of fluorescen proteins to visualize cancer in vivo"

22nd Annual Meeting of the Korean Society for Molecular and Cellular Biology — 2011
Seoul, Korea
Lecture entitled "The use of fluorescent proteins for cellular and subcellular imaging in live mice"

Idibell Cancer Conferences (ICC) on Mouse Models of Cancer — 2011
Barcelona, Spain
Lecture entitled "Orthotopic metastatic mouse models expressing fluorescent proteins for imaging metastasis at the macro and cellular level in real time"

4th Advances in Stem Cell Discovery and Development Conference — 2011
San Francisco, CA
Lecture entitled "Nestin-expressing cells from the dermal papilla and bulge area in the mouse vibrissa can equally repair spinal cord injury"

2nd Annual General Surgery Update 2011
Las Vegas, NV
Lecture entitled "Animal models of human cancer – what have we learned?"

74th Annual Meeting of the Japanese Dermatological Assocation 2011
Tokyo, Japan
Lecture entitled "In vivo imaging of dynamics of tumor growth, metastasis and angiogenesis"

Annual Meeting of the Society for Investigative Dermatology 2011
Phoenix, AZ
Lecture entitled "The bulge area is the major hair follicle source of nestin-expressing cells which can repair the spinal cord compared to the dermal papilla"

6th Workshop on Advanced Multiphoton & Fluorescence Lifetime Imaging Techniques (FLIM) 2011
Saarbrücken, Germany
Lecture entitled "The multiple uses of fluorescen proteins to visualize cancer in vivo"

7th Triennial International Union of Pure and Applied Physics 2011
La Jolla, CA
Lecture entitled "The multiple uses of fluorescen proteins to visualize cancer in vivo"

15th Annual Meeting of the European Hair Research Society 2011
Jerusalem, Israel
Lecture entitled "The bulge area is the major hair follicle source of nestin-expressing pluripotent stem cells"

III International Symposium on Topical Problems of Biophotonics 2011
Nizhny Novgorod, Russia
Lecture entitled "Imaging the in vivo cell biology of cancer"

21st International Pigment Cell Conference 2011
Bordeaux, France
Lecture entitled "Hair follicle pluripotent stsem (hfPS) cells for regenerative medicine:
an advantageous alternative to ES and iPS cells"

EXHIBIT A
39

Most Cited Publications of Robert M. Hoffman (1-100)
Total unique citations: 19,422 (ISI: 12,361) (Google: 16,627) (Scopus: 10,98
h-index = 75 (75 publications with at least 75 citations each)

1. Schmitt, C.A., Fridman, J.S., Yang, M., Lee, S., Baranov, E., Hoffman, R.M., and Lowe, S.W. A senescence program controlled by p53 and $p16^{INK4a}$ contributes to the outcome of cancer therapy. Cell **109**, 335-346, 2002. (Total unique citations: **554**) (ISI: 375) (Google: 500) (Scopus: 385)

2. Yang, M., Baranov, E., Jiang, P., Sun, F-X., Li, X-M., Li, L., Hasegawa, S., Bouvet, M., Al-Tuwaijri, M., Chishima, T., Shimada, H., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body optical imaging of green fluorescent protein-expressing tumors and metastases. Proc. Natl. Acad. Sci. USA **97**, 1206-1211, 2000. (Total unique citations: **472**) (ISI: 266) (Google: 429) (Scopus: 292)

3. Hoffman, R.M. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. A review and synthesis. Biochim. Biophys. Acta **738**, 49-87, 1984. (Total unique citations: **380**) (ISI: 293) (Google: 311) (Scopus: 23)

4. Schmitt, C.A., Fridman, J.S., Yang, M., Baranov, E., Hoffman, R.M. and Lowe, S.W. Dissecting p53 tumor suppressor functions in vivo. Cancer Cell **1**, 289-298, 2002 (Cover story). (Total unique citations: **357**) (ISI: 261) (Google: 329) (Scopus: 266)

5. Wang, X., Fu, X., Brown, P.D., Crimmin, M.J. and Hoffman, R.M. Matrix metalloproteinase inhibitor BB-94 (batimastat) inhibits human colon tumor growth and spread in a patient-like orthotopic model in nude mice. Cancer Res. **54**, 4726-4728, 1994. (Total unique citations: **301**) (ISI: 221) (Google: 241) (Scopus: 215)

6. Hoffman, R.M. The multiple uses of fluorescent proteins to visualize cancer *in vivo*. Nature Reviews Cancer **5**, 796-806, 2005. (Total unique citations: **293**) (ISI: 191) (Google: 264) (Scopus: 194)

7. Hoffman, R.M. Orthotopic metastatic mouse models for anticancer drug discovery and evaluation: a bridge to the clinic. Investigational New Drugs **17**, 343-359, 1999. (Total unique citations: **288**) (ISI: 157) (Google: 270) (Scopus: 168)

8. Chishima, T., Miyagi, Y., Wang, X., Yamaoka, H., Shimada, H., Moossa, A.R. and Hoffman, R.M. Cancer invasion and micrometastasis visualized in live tissue by green fluorescent protein expression. Cancer Research **57**, 2042-2047, 1997. (Total unique citations: **279**) (ISI: 173) (Google: 243) (Scopus: 183)

9. Glinsky, G.V., Glinskii, A.B., Stephenson, A.J., Hoffman, R.M., and Gerald, W.L. Gene expression profiling predicts clinical outcome of prostate cancer. J. Clin. Investig. **113**, 913-923, 2004. (Total unique citations: **242**) (ISI: 153) (Google: 223) (Scopus: 154)

10. Li, L., Hoffman, R.M. The feasibility of targeted selective gene therapy of the hair follicle. Nature Medicine **1**, 705-706, 1995. (Total unique citations: **235**) (ISI: 131) (Google: 211) (Scopus: 135)

11. Hoffman, R. Green fluorescent protein imaging of tumour growth, metastasis, and angiogenesis in mouse models. Lancet Oncology **3**, 546-556, 2002. (Total unique citations: **220**) (ISI: 132) (Google: 183) (Scopus: 151)

12. Furukawa, T., Fu, X., Kubota, T., Watanabe, M., Kitajima, M. and Hoffman, R.M. Nude mouse metastatic models of human stomach cancer constructed using orthotopic transplantation of histologically intact tissue. Cancer Res. **53**, 1204-1208, 1993. (Total unique citations: **215**) (ISI: 91) (Google: 184) (Scopus: 77)

13. Fu, X.Y., Besterman, J.M., Monosov, A. and Hoffman, R.M. Models of human metastatic colon cancer in nude mice orthotopically constructed by using histologically intact pa161ient specimens. Proc. Natl. Acad. Sci. USA **88**, 9345-9349, 1991. (Total unique citations: **208**) (ISI: 156) (Google: 161) (Scopus: 112)

14. Yang, M., Baranov, E., Moossa, A.R., Penman, S., Hoffman, R.M. Visualizing gene expression by whole-body fluorescence imaging. Proc. Natl. Acad. Sci. USA **97**, 12278-12282, 2000. (Total unique citations: **203**) (ISI: 96) (Google: 184) (Scopus: 115)

15. Amoh, Y., Li, L., Katsuoka, K., Penman, S., and Hoffman, R.M. Multipotent nestin-positive, keratin-negative hair-follicle-bulge stem cells can form neurons. Proc. Natl. Acad. Sci. USA **102**, 5530-5534, 2005. (Total unique citations: **203**) (ISI: 137) (Google: 180) (Scopus: 135)

16. Fu, X., Guadagni, F. and Hoffman, R.M. A metastatic nude-mouse model of human pancreatic cancer constructed orthotopically from histologically intact patient specimens. Proc. Natl. Acad. Sci. USA **89**, 5645-5649, 1992. (Total unique citations: **189**) (ISI: 124) (Google: 154) (Scopus: 109)

17. Furukawa, T., Kubota, T., Hoffman, R.M. Clinical applications of the histoculture drug response assay. Clinical Cancer Research **1**, 305-311, 1995. (Total unique citations: **179**) (ISI: 108) (Google: 145) (Scopus: 126)

18. Li, L., Mignone, J., Yang, M., Matic, M., Penman, S., Enikolopov, G., and Hoffman, R.M. Nestin expression in hair follicle sheath progenitor cells. Proc. Natl. Acad. Sci. USA **100**, 9958-9961, 2003. (Total unique citations: **176**) (ISI: 123) (Google: 155) (Scopus: 120)

19. Hoffman, R.M. and Erbe, RW. High *in vivo* rates of methionine biosynthesis in transformed human and malignant rat cells auxotrophic for methionine. Proc. Natl. Acad. Sci. USA **73**, 1523-1527, 1976. (Total unique citations: **173**) (ISI: 141) (Google: 143) (Scopus: 52)

20. Yang, M., Jiang, P., Sun, F.X., Hasegawa, S., Baranov, E., Chishima, T., Shimada, H., Moossa, A.R., and Hoffman, R.M. A fluorescent orthotopic bone metastasis model of human prostate cancer. Cancer Research **59**, 781-786, 1999. (Total unique citations: **171**) (ISI: 113) (Google: 156) (Scopus: 114)

21. Freeman, A.E. and Hoffman, R.M. In vivo-like growth of human tumors in vitro. Proc. Natl. Acad. Sci. USA **83**, 2694-2698, 1986. (Total unique citations: **170**) (ISI: 114) (Google: 134) (Scopus: 49)

22. Yang, M., Baranov, E., Wang, J-W., Jiang, P., Wang, X., Sun, F-X., Bouvet, M., Moossa, A.R., Penman, S., and Hoffman, R.M. Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model. Proc. Natl. Acad. Sci. USA **99**, 3824-3829, 2002. (Total unique citations: **167**) (ISI: 90) (Google: 146) (Scopus: 102)

23. Naumov, G.N., Wilson, S.M., MacDonald, I.C., Schmidt, E.E., Morris, V.L., Groom, A.C., Hoffman, R.M., Chambers, A.F. Cellular expression of green fluorescent protein, coupled with high-resolution *in vivo* videomicroscopy, to monitor steps in tumor metastasis. J. Cell Sci. **112**, 1835-1842, 1999. (Total unique citations: **162**) (ISI: 113) (Google: 147) (Scopus: 116)

24. Simberg, D., Duza, T., Park, J.H., Essler, M., Pilch, J., Zhang, L., Derfus, A.M., Yang, M., Hoffman, R.M., Bhatia, S., Sailor, M.J., and Ruoslahti, E. Biomimetic amplification of nanoparticle homing to tumors. Proc. Natl. Acad. Sci. USA **104**, 932-936, 2007. (Total unique citations: **161**) (ISI: 99) (Google: 148) (Scopus: 106)

25. Amoh, Y., Li, L., Campillo, R., Kawahara, K., Katsuoka, K., Penman, S., and Hoffman, R.M. Implanted hair follicle stem cells form Schwann cells that support repair of severed peripheral nerves. Proc. Natl. Acad. Sci. USA **102**, 17734-17738, 2005. (Total unique citations: **155**) (ISI: 96) (Google: 130) (Scopus: 97)

26. Bouvet, M., Wang, J-W., Nardin, S.R., Nassirpour, R., Yang, M., Baranov, E., Jiang, P., Moossa, A.R., and Hoffman, R.M. Real-time optical imaging of primary tumor growth and multiple metastatic events in a pancreatic cancer orthotopic model. Cancer Research **62**, 1534-1540, 2002 (Cover story). (Total unique citations: **154**) (ISI: 81) (Google: 132) (Scopus: 102)

27. Cheah, M.S., Wallace, C.D. and Hoffman, R.M. Hypomethylation of DNA in human cancer cells: a site-specific change in the c-myc oncogene. J. Natl. Cancer Inst. **73,** 1057-1065, 1984. (Total unique citations: **150**) (ISI: 111) (Google: 113) (Scopus: 50)

28. Hoffman, R.M. Three-dimensional histoculture: origins and applications in cancer research. Cancer Cells **3,** 86-92, 1991 (Cover story). (Total unique citations: **144**) (ISI: 92) (Google: 118) (Scopus: 51)

29. Kubota, T., Sasano, N., Abe, O., Nakao, I., Kawamura, E., Saito, T., Endo, M., Kimura, K., Demura, H., Sasano, H., Nagura, H., Ogawa, N., Hoffman, R.M. Potential of the histoculture drug response assay to contribute to cancer patient survival. Clinical Cancer Research **1**, 1537-1543, 1995. (Total unique citations: **142**) (ISI: 89) (Google: 91) (Scopus: 108)

30. Hoffman, R.M. Altered methionine metabolism and transmethylation in cancer. Anticancer Res. **5,** 1-30, 1985. (Total unique citations: **140**) (ISI: 79) (Google: 125) (Scopus: 45)

31. Yang, M., Baranov, E., Li., X-M., Wang, J-W., Jiang, P., Li, L., Moossa, A.R., Penman, S., Hoffman, R.M. Whole-body and intravital optical imaging of angiogenesis in orthotopically implanted tumors. Proc. Natl. Acad. Sci. USA **98,** 2616-2621, 2001. (Total unique citations: **140**) (ISI: 80) (Google: 126) (Scopus: 85)

32. Vescio, R.A., Redfern, C.H., Nelson, T.J., Ugoretz, S. Stern, P.H. and Hoffman, R.M. *In vivo*-like drug responses of human tumors growing in three-dimensional gel-supported, primary culture. Proc. Natl. Acad. Sci. USA **84,** 5029-5033, 1987. (Total unique citations: **137**) (ISI: 88) (Google: 109) (Scopus: 48)

33. Yang, M., Hasegawa, S., Jiang, P., Wang, X., Tan, Y., Chishima, T., Shimada, H., Moossa, A.R., and Hoffman, R.M. Widespread skeletal metastatic potential of human lung cancer revealed by green fluorescent protein expression. Cancer Research **58**, 4217-4221, 1998. (Total unique citations: **137**) (ISI: 82) (Google: 122) (Scopus: 88)

34. Zhao, M., Yang, M., Li, X-M., Jiang, P., Li, S., Xu, M., and Hoffman, R.M. Tumor-targeting bacterial therapy with amino acid auxotrophs of GFP-expressing *Salmonella typhimurium.* Proc. Natl. Acad. Sci. USA **102**, 755-760, 2005. DOI: 10.1073/pnas 0408422102. (Total unique citations: **131**) (ISI: 85) (Google: 120) (Scopus: 78)

35. Yang, M., Li, L., Jiang, P., Moossa, A.R., Penman, S., and Hoffman, R.M. Dual-color fluorescence imaging distinguishes tumor cells from induced host angiogenic vessels and stromal cells. Proc. Natl. Acad. Sci. USA **100**, 14259-14262, 2003. (Total unique citations: **128**) (ISI: 77) (Google: 120) (Scopus: 83)

36. Amoh, Y., Li, L., Yang, M., Moossa, A.R., Katsuoka, K., Penman, S., and Hoffman, R.M. Nascent blood vessels in the skin arise from nestin-expressing hair follicle cells. Proc. Natl. Acad. Sci. USA **101**, 13291-13295, 2004. (Total unique citations: **123**) (ISI: 83) (Google: 110) (Scopus: 78)

37. Furukawa, T., Kubota, T., Watanabe, M., Takahara, T., Yamaguchi, H., Takeuchi, T., Kase, S., Kodaira, S., Ishibiki, K., Kitajima, M. and Hoffman, R.M. High *in vitro-in vivo* correlation of drug response using sponge-gel-supported three-dimensional histoculture and the MTT end point. Int. J. Cancer **51**, 489-498, 1992. (Total unique citations: **121**) (ISI: 66) (Google: 91) (Scopus: 53)

38. Guo, H-Y., Herrera, H., Groce, A., and Hoffman, R.M. Expression of the biochemical defect of methionine dependence in fresh patient tumors in primary histoculture. Cancer Res. **53**, 2479-2483, 1993. (Total unique citations: **118**) (ISI: 76) (Google: 103) (Scopus: 70)

39. Berezovskaya, O., Schimmer, A.D., Glinskii, A.B., Pinilla, C., Hoffman, R.M., Reed, J.C., and Glinsky, G.V. Increased expression of apoptosis inhibitor protein XIAP contributes to anoikis resistance of circulating human prostate cancer metastasis precursor cells. Cancer Research **65**, 2378-2386, 2005. (Total unique citations: **118**) (ISI: 82) (Google: 103) (Scopus: 81)

40. Geller, J., Sionit, L., Partido, C., Li, L., Tan, XY., Youngkin, T., Nachtsheim, D. and Hoffman, R.M. Genistein inhibits the growth of human-patient BPH and prostate cancer in histoculture. The Prostate **34**, 75-79, 1998. (Total unique citations: **117**) (ISI: 59) (Google: 106) (Scopus: 65)

41. Pfeifer, A., Kessler, T., Yang, M., Baranov, E., Kootstra, N., Cheresh, D.A., Hoffman, R.M., and Verma, I.M. Transduction of liver cells by lentiviral vectors: analysis in living animals. Molecular Therapy **3**, 319-322, 2001. (Total unique citations: **117**) (ISI: 71) (Google: 105) (Scopus: 74)

42. Laakkonen, P., Akerman, M.E., Biliran, H., Yang, M., Ferrer, F., Karpanen, T., Hoffman, R.M., and Ruoslahti, E. Antitumor activity of a homing peptide that targets tumor lymphatics and tumor cells. Proc. Natl. Acad. Sci. USA **101**, 9381-9386, 2004. (Total unique citations: **117**) (ISI: 66) (Google: 109) (Scopus: 60)

43. Mecham, J.O., Rowitch, D., Wallace, C.D., Stern, P.H. and Hoffman, R.M. The metabolic defect of methionine dependence occurs frequently in human tumor cell lines. Biochem. Biophys. Res. Commun. **117,** 429-434, 1983. (Total unique citations: **115**) (ISI: 96) (Google: 94) (Scopus: 49)

44. Zhang, L., Li, L., Hoffmann, G.A., Hoffman, R.M. Depth-targeted efficient gene delivery and expression in the skin by pulsed electric fields: an approach to gene therapy of skin aging and other diseases. Biochem. Biophys. Res. Commun. **220**, 633-636; 1996. (Total unique citations: **115**) (ISI: 63) (Google: 100) (Scopus: 63)

45. Diala, E.S., Cheah, M.S.C., Rowitch, D. and Hoffman, R.M. Extent of DNA methylation in human tumor cells. J. Natl. Cancer Inst. **71**, 755-764, 1983. (Total unique citations: **112**) (ISI: 88) (Google: 85) (Scopus: 32)

46. Chishima, T., Miyagi, Y., Wang, X., Baranov, E., Tan, Y., Shimada, H., Moossa, A.R., and Hoffman, R.M. Metastatic patterns of lung cancer visualized live and in process by green fluorescent protein expression. Clinical & Experimental Metastasis **15**, 547-552, 1997. (Total unique citations: **107**) (ISI: 65) (Google: 92) (Scopus: 65)

47. Chishima, T., Yang, M., Miyagi, Y., Li, L., Tan, Y., Baranov, E., Shimada, H., Moossa, A.R., Penman, S., Hoffman, R.M. Governing step of metastasis visualized *in vitro.* Proc. Natl. Acad. Sci. USA **94**, 11573-11576, 1997. (Total unique citations: **107**) (ISI: 53) (Google: 95) (Scopus: 59)

48. Goodison, S., Kawai, K., Hihara, J., Jiang, P., Yang, M., Urquidi, V., Hoffman, R.M., and Tarin, D. Prolonged dormancy and site-specific growth potential of cancer cells spontaneously disseminated from nonmetastatic breast tumors as revealed by labeling with green fluorescent protein. Clinical Cancer Res. **9**, 3808-3814, 2003. (Total unique citations: **102**) (ISI: 73) (Google: 94) (Scopus: 78)

49. Fu, X. and Hoffman, R.M. Human ovarian carcinoma metastatic models constructed in nude mice by orthotopic transplantation of histologically-intact patient specimens. Anticancer Res. **13**, 283-286, 1993. (Total unique citations: **98**) (ISI: 48) (Google: 87) (Scopus: 51)

50. Hoffman, R.M. *In vitro* sensitivity assays in cancer: A review, analysis and prognosis. J. Clin. Lab. Anal. **5**, 133-143, 1991. (Total unique citations: **94**) (ISI: 70) (Google: 80) (Scopus: 50)

51. Yamauchi, K., Yang, M., Jiang, P., Xu., M., Yamamoto, N., Tsuchiya, H., Tomita, K., Moossa, A.R., Bouvet, M., and Hoffman, R.M. Development of real-time subcellular dynamic multicolor imaging of cancer cell-trafficking in live mice with a variable-magnification whole-mouse imaging system. Cancer Res. **66**, 4208-4214, 2006. (Total unique citations: **94**) (ISI: 69) (Google: 82) (Scopus: 73)

52. Hoffman, R.M., Connors, K.M., Meerson-Monosov, A.Z, Herrera, H. and Price, J.H. A general native-state method for determination of proliferation capacity of human normal and tumor tissues *in vitro*. Proc. Natl. Acad. Sci. USA **86**, 2013-2017, 1989. (Total unique citations: **93**) (ISI: 67) (Google: 67) (Scopus: 28)

53. Wang, X., Fu, X. and Hoffman, R.M. A new patient-like metastatic model of human lung cancer constructed orthotopically with intact tissue via thoracotomy in immunodeficient mice. Int. J. Cancer **51**, 992-995, 1992. (Total unique citations: **93**) (ISI: 69) (Google: 70) (Scopus: 43)

54. Hoffman, R.M. To do tissue culture in two or three dimensions? That is the question. Stem Cells **11**, 105-111, 1993. (Total unique citations: **93**) (ISI: 58) (Google: 85) (Scopus: 52)

55. Berezovska, O.P., Glinskii, A.B., Yang, Z., Li, X.M., Hoffman, R.M., and Glinsky, G.V. Essential role for activation of the Polycomb Group (PcG) protein chromatin silencing pathway in metastatic prostate cancer. Cell Cycle **5**, 1886-1901, 2006. (Total unique citations: **91**) (ISI: 50) (Google: 81) (Scopus: 57)

56. Stern, P.H., Wallace, C.D. and Hoffman, R.M. Altered methionine metabolism occurs in all members of a set of diverse human tumor cell lines. J. Cell. Physiol. **119**, 29-34, 1984. (Total unique citations: **89**) (ISI: 66) (Google: 73) (Scopus: 35)

57. Hoffman, R.M. Orthotopic is orthodox: why are orthotopic-transplant metastatic models different from all other models? J. Cell. Biochem. **56**, 1-3, 1994. (Total unique citations: **89**) (ISI: 52) (Google: 68) (Scopus: 48)

58. Chishima, T., Miyagi, Y., Wang, X., Tan, Y., Shimada, H., Moossa, A.R. and Hoffman, R.M. Visualization of the metastatic process by green fluorescent protein expression. Anticancer Research **17**, 2377-2384, 1997. (Total unique citations: **88**) (ISI: 48) (Google: 79) (Scopus: 52)

59. Fu, X., Herrera, H. and Hoffman, R.M. Orthotopic growth and metastasis of human prostate carcinoma in nude mice after transplantation of histologically intact tissue. Int. J. Cancer **52**, 987-990, 1992. (Total unique citations: **87**) (ISI: 58) (Google: 75) (Scopus: 47)

60. Yamamoto, N., Jiang, P., Yang, M., Xu, M., Yamauchi, K., Tsuchiya, H., Tomita, K., Wahl, G.M., Moossa, A.R., and Hoffman, R.M. Cellular dynamics visualized in live cells *in vitro* and *in vivo* by differential dual-color nuclear-cytoplasmic fluorescent-protein expression. Cancer Research **64**, 4251-4256, 2004. (Total unique citations: **87**) (ISI: 59) (Google: 76) (Scopus: 62)

61. Hoffman, R.M. Topical liposome targeting of dyes, melanin, genes and proteins selectively to hair follicles. J. Drug Targeting, **5**, 67-74, 1998. (Total unique citations: **86**) (ISI: 33) (Google: 79) (Scopus: 44)

62. Amoh, Y., Yang, M., Li, L., Reynoso, J., Bouvet, M., Moossa, A.R., Katsuoka, K., and Hoffman, R.M. Nestin-linked green fluorescent protein transgenic nude mouse for imaging human tumor angiogenesis. Cancer Res. **65**, 5352-5357, 2005. (Total unique citations: **86**) (ISI: 59) (Google: 75) (Scopus: 59)

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EXHIBIT B

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 1, pp. 446–454, January 2, 2012

Structure-guided Engineering of Human Thymidine Kinase 2 as a Positron Emission Tomography Reporter Gene for Enhanced Phosphorylation of Non-natural Thymidine Analog Reporter Probe*[S]

Received for publication, October 17, 2011, and in revised form, November 9, 2011 Published, JBC Papers in Press, November 10, 2011, DOI 10.1074/jbc.M111.314666

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Background: Humanized PET reporter gene (PRG) systems are needed to replace immunogenic, viral-derived systems.
Results: Employing a structure-guided approach, we developed a highly sensitive humanized PRG characterized by reduced activity for its natural substrates.
Conclusion: Sensitivity of PRGs can be improved by reducing their endogenous activities.
Significance: Our method can be employed to rapidly develop highly sensitive humanized PRGs.

Positron emission tomography (PET) reporter gene imaging can be used to non-invasively monitor cell-based therapies. Therapeutic cells engineered to express a PET reporter gene (PRG) specifically accumulate a PET reporter probe (PRP) and can be detected by PET imaging. Expanding the utility of this technology requires the development of new non-immunogenic PRGs. Here we describe a new PRG-PRP system that employs, as the PRG, a mutated form of human thymidine kinase 2 (TK2) and 2′-deoxy-2′-^{18}F-5-methyl-1-β-L-arabinofuranosyluracil (L-^{18}F-FMAU) as the PRP. We identified L-^{18}F-FMAU as a candidate PRP and determined its biodistribution in mice and humans. Using structure-guided enzyme engineering, we generated a TK2 double mutant (TK2-N93D/L109F) that efficiently phosphorylates L-^{18}F-FMAU. The N93D/L109F TK2 mutant has lower activity for the endogenous nucleosides thymidine and deoxycytidine than wild type TK2, and its ectopic expression in therapeutic cells is not expected to alter nucleotide metabolism. Imaging studies in mice indicate that the sensitivity of the new human TK2-N93D/L109F PRG is comparable with that of a widely used PRG based on the herpes simplex virus 1 thymidine kinase. These findings suggest that the TK2-N93D/L109F/L-^{18}F-FMAU PRG-PRP system warrants further evaluation in preclinical and clinical applications of cell-based therapies.

The inability to routinely monitor the tissue pharmacokinetics of therapeutic genes and cells and correlate this information with therapeutic outcomes represents a significant roadblock in the clinical adoption of these emerging therapies. Most cell/gene therapy trials use invasive biopsy techniques to localize therapeutic genes or therapeutic cells at target sites. However, invasive techniques are prone to sampling errors and carry risks for the patients. There is an unmet need for techniques to monitor the whole-body tissue distribution of therapeutic cells and therapeutic genes, to quantify therapeutic cells, and to measure therapeutic gene expression at all locations non-invasively and sequentially after treatment. This unmet need can be addressed by PET[3] reporter gene (PRG) imaging (1). A PRG encodes a protein that mediates the specific accumulation of a PET reporter probe (PRP) labeled with a positron-emitting isotope (2). Such non-invasive PET measurements may predict and/or evaluate treatment efficacy and the risk of side effects; they can provide information that complements data obtained using invasive techniques, such as serial biopsies (2). PRGs developed

* This work was supported, in whole or in part, by National Institutes of Health Grants P50 CA86306 (In Vivo Cellular and Molecular Imaging Centers Developmental Project) 1R01EB13685 and 1R01CA16077001 (National Institute of Biomedical Imaging and Bioengineering). This work was also funded by California Institute for Regenerative Medicine Grant RT1-01126-1 and United States Department of Energy Contract DE-FG02-06ER64249. Conflict of interest statement: Dean Campbell, Caius Radu, Arnon Lavie, Nagichettiar Satyamurthy, Johannes Czernin, and Shahriar Yaghoubi are among the inventors of the national and Patent Cooperation Treaty (PCT) patent applications for the PRG technology referred to in this article. Shahriar Yaghoubi is also a co-founder and the Chief Scientific Officer of CellSight Technologies, Inc., a molecular imaging company that specializes in imaging tools for cell and gene therapies that has licensed this intellectual property.
[S] This article contains supplemental Tables 1–3.
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[3] The abbreviations used are: PET, positron emission tomography; PRG, PET reporter gene; PRP, PET reporter probe; TK2, thymidine kinase 2; L-^{18}F-FMAU, 2′-deoxy-2′-^{18}F-5-methyl-1-β-L-arabinofuranosyluracil; HSV1-tk, herpes simplex virus type 1 thymidine kinase; ^{18}F-FHBG, 9-[4-^{18}F-3-(hydroxymethyl)butyl]guanine; CT, computed tomography; GI, gastrointestinal; D-dT, D-thymdine; L-dT, L-thymidine; SUMO, small ubiquitin-like modifier; dCK, deoxycytidine kinase.

EXHIBIT A
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to date encode proteins with various activities, including enzymes, transporters, and receptors (for review, see Ref. 3). In theory, enzyme-encoding PRGs should have the highest sensitivity among different classes of PRGs as a result of signal amplification by the catalytic turnover of the enzymatic reaction that traps the probe. The most commonly used PRGs are based on herpes simplex virus type 1 thymidine kinase (HSV1-tk) (4) and its optimized mutant, sr39tk (5). Both wild type (WT) HSV1-tk and sr39tk have been used to study the kinetics of therapeutic cells in preclinical settings (6–9). Several PRPs can be used to image cells engineered to express HSV1-tk-based PRGs: 9-[4-^{18}F-3-(hydroxymethyl)butyl]guanine (^{18}F-FHBG) (10–12), 2′-deoxy-2′-^{18}F-5-ethyl-1-β-D-arabinofuranosyluracil (^{18}F-FEAU) (13–15), and 2′-deoxy-2′-^{18}F-5-iodo-1-β-D-arabinofuranosyluracil (^{18}F-FIAU) (15). To date, HSV1-tk is the only PRG that has been used to image therapeutic cells in patients (10).

The main disadvantage of HSV1-tk as a PRG is its immunogenicity, which can lead to immune-mediated elimination of therapeutic cells. This phenomenon has been documented in clinical trials (16, 17). The immunogenicity problem may be solved by replacing the viral kinase with a human orthologue (18). Two potentially non-immunogenic candidate PRGs based on human nucleoside kinases have been developed; that is, a double mutant of deoxycytidine kinase (dCK) (19) and a truncated form of mitochondrial thymidine kinase 2 (TK2) (20). These PRGs phosphorylate and trap the PRP ^{18}F-FEAU. The sensitivity of the dCK-double mutant/^{18}F-FEAU PRG-PRP system was comparable with that of HSV1-tk/^{18}F-FEAU, whereas TK2/^{18}F-FEAU had lower sensitivity. In non-human primates ^{18}F-FEAU has a favorable biodistribution as a candidate PRP, with tracer accumulation in the liver, small intestine, kidneys, and urinary bladder (21) but not in other organs and tissues. Human biodistribution data for this candidate PRP are not available.

The utility of a PRG-PRP system is dependent on its sensitivity (the ability to detect few therapeutic cells at various anatomical locations) and specificity (the probe should accumulate only in cells engineered to express the PRG). Another equally important parameter is the requirement that a PRG should be biologically inert. In other words its ectopic expression in therapeutic cells should not alter the metabolism or normal function of these cells. This requirement is especially important in the case of nucleoside kinase PRGs. Ectopic expression of a nucleoside kinase could perturb the normal regulation of nucleotide metabolism through excess phosphorylation of endogenous nucleosides. Such metabolic alterations can lead to imbalanced nucleotide pools and increased risk of genotoxicity (22–25). In this context the dCK-double mutant has significantly higher activity than WT dCK toward endogenous nucleosides such as deoxycytidine and thymidine (26). Truncated TK2 also retains normal activity with natural substrates. Whether these new PRGs fulfill the critical requirement of being biologically inert remains to be determined.

Here we describe the development of a new PRG-PRP system that meets the specifications mentioned above. We determined the biodistribution of L-^{18}F-FMAU, the candidate PRP, in mice and humans. We used enzyme engineering to develop a mutant PRG enzyme that is orthogonal to the wild type enzyme regarding its ability to phosphorylate endogenous nucleosides. The resulting PRG-PRP system, TK2-N93D/L109F as PRG and L-^{18}F-FMAU as PRP, should find utility in various preclinical and clinical therapeutic cell tracking applications. The approach used to develop this system should be generalizable to the identification and evaluation of other pairs of nucleoside analogs and nucleoside kinases for PET reporter gene imaging applications.

EXPERIMENTAL PROCEDURES

Radiochemical Synthesis of ^{18}F-Labeled PET Probes—^{18}F-FHBG was synthesized as previously described (12). The radiochemical synthesis of L-^{18}F-FMAU is described in the supplemental material.

Molecular Modeling of Human TK2—We generated a homology model of TK2 using the SWISS-MODEL server (27). The solved structures of human dCK (35% identity, 50% homology to TK2) in both its closed (PDB ID 1P5Z) and open conformation (PDB ID 3QEO) (28, 29) served as templates.

Generation of TK2 Mutants—We used the Δ50N truncation variant of TK2, and we are referring to this truncated form (which lacks the mitochondrial sorting signal) as the WT enzyme. Numbering of residues is based on the full-length sequence of human TK2 (Uniprot ID O00142). Cloning of human TK2 has been described previously (30). Mutants were produced on the WT TK2 sequence that was present in both the pMSCV vector for retroviral transduction and a modified pET14b expression vector for production of recombinant protein.

Expression and Purification of Recombinant TK2 Proteins—Expression and purification of TK2 have been described previously (30). In short, *Escherichia coli* BL21 (DE3) C41 harboring the modified pET14b vector (to include a SUMO tag between the hexahistidine sequence and TK2) were grown at 37 °C until an optical density of ~0.8 was reached. At that point the temperature was reduced to 18 °C; the culture was induced with 0.5 mM isopropyl β-D-1-thiogalactopyranoside and left to shake overnight. Cells were harvested by centrifugation, washed, and stored at −80 °C until use. Purification involved two steps. The first step used a metal affinity column (HisTRAP HP column, GE Healthcare); after elution of the His-SUMO-TK2 fusion protein, the SUMO protease was added. The cleaved protein was reapplied onto the nickel column to separate TK2 from the His-SUMO tag. The second step involved a gel filtration column (S200, GE Healthcare) equilibrated with 25 mM Tris, pH 7.5, 200 mM NaCl, and 3 mM DTT. Pure TK2 was pooled, concentrated to ~10 mg/ml, separated into aliquots, flash-frozen in liquid nitrogen, and stored at −80 °C until use.

Kinetic Analyses of TK2-based Candidate PRGs—We used an NADH-dependent enzyme coupled assay (31). Using a Cary UV spectrophotometer, measurements were made in triplicate at 37 °C in a buffer containing 100 mM Tris, pH 7.5, 100 mM KCl, 5 mM $MgCl_2$, and 1 mM ATP. For data in which k_{obs} is given, a single nucleoside concentration of 200 μM was used. For data in which both K_m and k_{cat} are given, the nucleoside concentration was varied between 15 and 500 μM. TK2 concentration in the cuvette was 400 nM. Data were fit to the Michaelis-Menten

equation using SigmaPlot. Of note, in some previous reports, negative cooperativity was observed with thymidine but not with deoxycytidine (32, 33). When we fit our data for WT TK2 using the Hill equation, we also see the same magnitude of negative cooperativity as reported by others ($n = \sim 0.7$) with thymidine and the analogs tested. However, the quality of the fit of the data is only marginally improved compared with that using the simple Michaelis-Menten equation. When the data of the TK2 mutants are fit using the Hill equation, a more complicated behavior is observed, with some conditions having a Hill coefficient below 1, some above 1, and some nearly one. Here again, the quality of the fit is not dramatically improved by adding the extra parameter of the Hill coefficient. Therefore, we present all of the kinetic data using the Michaelis-Menten equation without the Hill coefficient.

Cell Lines—The L1210 cell line (34) was a gift from Charles Dumontet (Université Claude Bernard Lyon I, Lyon, France). Cells were cultured at 5% v/v CO_2 and 37 °C in RPMI supplemented with 5% v/v FCS. Murine stem cell virus (pMSCV)-based helper-free retroviruses encoding the TK2 mutants (or sr39tk), an internal ribosomal entry site, and the yellow fluorescent protein (YFP) were produced by transient co-transfection of the amphotrophic retrovirus packaging cell line Phoenix (American Type Culture Collection, SD 3443) (35). L1210 cells underwent spinfection with the pMSCV-TK2 mutants- internal ribosomal entry site-YFP retrovirus with 2 μg/ml Polybrene (1000 × *g*, 120 min, 37 °C). L1210 cells expressing various PRGs, (L1210-PRG) were FACS-sorted to ensure that each population had equivalent levels of PRG expression.

Probe Uptake Assays Using Transduced L1210 Cell Lines—L1210 cells transduced with the indicated PET reporter genes (L1210-PRG) were seeded at a density of 500,000 cells/well in 24-well plates. 5 μCi of L-^{18}F-FMAU were added to the L1210-PRG cells simultaneously with the indicated amounts of D-thymidine (D-dT) at a final volume of 1 ml/well. After 1 h at 37 °C, cells were harvested and washed four times with ice-cold PBS. Radioactivity was measured using a gamma counter.

MicroPET/CT Imaging Studies in Mice—Animal studies were approved by the UCLA Animal Research Committee and were carried out according to the guidelines of the Department of Laboratory Animal Medicine at UCLA. C57/BL6 mice were injected with the indicated probe and underwent microPET/CT analyses at 1- and 3-h post probe injection (Inveon, Siemens Medical Solutions USA Inc.; microCAT; Imtek Inc.). For tumor imaging studies, SCID mice were injected subcutaneously on day −7 in the right and left flanks with 1×10^6 L1210-PRG-expressing cells in 50% v/v phosphate-buffered saline and 50% v/v Matrigel™ (BD Biosciences). For imaging experiments, mice were kept warm and under gas anesthesia (2% v/v isoflurane) and were injected intravenously with 200 μCi of ^{18}F-labeled probes. A 3-h interval was allowed between probe administration and microPET/CT scanning. Static microPET images were acquired for 600 s. Image data were evaluated in three-dimensional histograms and reconstructed with a zoom factor of 2.1 using three-dimensional ordered set expectation maximization (OSEM) with 2 iterations followed by MAP (maximum a posteriori) reconstruction with 18 iterations (beta = 0.1). Images were analyzed using OsiriX Imaging Software Version 3.8.

Human PET/CT Studies—All studies involving human volunteers were approved by the UCLA Medical Internal Review Board. L-^{18}F-FMAU was approved by the UCLA Radioactive Drug Research Committee. L-^{18}F-FHBG has an FDA investigational new drug approval (IND #61,880) and was also approved by the UCLA Radioactive Drug Research Committee. A 53-year-old healthy male and a 44-year-old healthy female volunteer were recruited for the L-^{18}F-FMAU biodistribution study. Each volunteer received a bolus intravenous injection of ~56 MBq (1.5 mCi) sterile L-^{18}F-FMAU and had four consecutive whole-body (starting from just above the head to above the knees, 6 bed positions, 5-min scan at each bed position) PET scans (Biograph 64, Siemens), with the first scan starting shortly after intravenous injection of L-^{18}F-FMAU. A low dose CT scan was also obtained for attenuation correction. Volunteers urinated after all scans had been performed. The region of interest analysis was performed to measure mean standard uptake values of L-^{18}F-FMAU in major organs/tissues. To illustrate the biodistribution of ^{18}F-FHBG, we used an unpublished scan from a previous study (10).

Statistical Analysis—Data are presented as the means ± S.E. All *p* values are two-tailed, and *p* values of <0.05 are considered to be statistically significant. Graphs were generated and analyzed using the Prism 5 software (GraphPad).

RESULTS

Comparison of Biodistribution of L-^{18}F-FMAU and ^{18}F-FHBG in Mice—Nucleoside analogs are being increasingly used as PET probes for assaying nucleotide metabolism, cell proliferation, and mitochondrial function (36–40). Nucleosides can adopt one of two enantiomeric configurations. Naturally occurring nucleosides are in the D configuration (41). Recently there has been increasing interest in using nucleoside analogs with the non-natural L configuration as PET probes to image the activity of endogenous nucleoside kinases (42–45). To date, L nucleosides have not been evaluated as PRPs. To start determining the potential value of L nucleosides as PRPs, we focused on L-^{18}F-FMAU, the non-natural counterpart of D-^{18}F-FMAU, one of the pyrimidine analogs that has been previously evaluated as a candidate PRP for the HSV1-tk PRG (46).

We compared the biodistribution of L-^{18}F-FMAU in mice with that of ^{18}F-FHBG, a well characterized and frequently used PRP (12, 47, 48). To achieve optimal signal to noise ratios, PRPs should not accumulate in cells and tissues that do not express the corresponding PRG. For instance, the accumulation of the candidate PRP should be minimal or undetectable in all tissues, except in those involved in probe clearance from the body. C57/BL6 mice were scanned 3 h after administration of either L-^{18}F-FMAU or ^{18}F-FHBG (Fig. 1*A*). Three-dimensional reconstructions of the whole body microPET/CT images are shown in Fig. 1*B*. Quantification of the signals is presented in supplemental Table 1. Both L-^{18}F-FMAU and ^{18}F-FHBG had very low retention in the thoracic cavity. At the 3-h time point neither probe showed any accumulation in the liver. Accumulation in the gallbladder was 4 times higher for ^{18}F-FHBG (7.45 ± 5.31% injected dose/g) than for L-^{18}F-FMAU (1.68 ± 0.46% injected

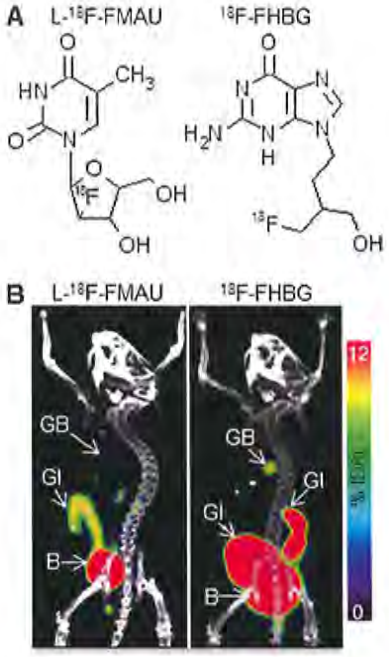

FIGURE 1. **Biodistribution of L-^{18}F-FMAU and ^{18}F-FHBG in mice.** *A*, chemical structures of L-^{18}F-FMAU and ^{18}F-FHBG are shown. *B*, MicroPET/CT scans of C57/BL6 mice 3 h after injection of L-^{18}F-FMAU (*left*) and ^{18}F-FHBG (*right*) are shown. Images are co-registered displays of the separate microPET and microCT scans. Quantifications of the PET signals are listed in supplemental Table 1. *B*, bladder; *GB*, gallbladder. *%ID/g*, % injected dose/g.

dose/g). Retention in the abdominal cavity was three times higher for ^{18}F-FHBG than for L-^{18}F-FMAU. This was likely due to higher biliary excretion of ^{18}F-FHBG. Elevated ^{18}F-FHBG accumulation was detected throughout the GI tract. In contrast, in mice injected with L-^{18}F-FMAU signals were only detected in the lower GI tract. Thus, the biodistribution of L-^{18}F-FMAU in mice was at least comparable with, if not better than that of ^{18}F-FHBG.

Development of New PRG to Be Used in Conjunction with L-^{18}F-FMAU Candidate PRP—L-FMAU has been shown to be a substrate for human TK2, a nucleoside kinase that due to its lack of enantiomeric specificity can phosphorylate both D and L nucleosides (49). Ideally, modifications to the TK2 sequence should achieve two objectives; (i) increase sensitivity by reducing the negative feedback regulation of the enzyme and by increasing the phosphorylation rate of the L-FMAU PRP; (ii) reduce the activity of the PRG kinase for the endogenous substrates thymidine and deoxycytidine (to avoid competition between L-FMAU and endogenous nucleosides and potentially genotoxic perturbations of endogenous nucleotide pools).

The enzymatic activity of TK2 is regulated by thymidine triphosphate (dTTP) through negative feedback inhibition (50). dTTP is produced by *de novo* synthesis and through the salvage of thymidine (via the cytosolic nucleoside kinase TK1). dTTP levels fluctuate throughout the cell cycle and are highest during the S phase, when they increase by as much as 2.5–20-fold compared with the G_1 phase (51, 52). It is possible that fluctuations in dTTP levels during the cell cycle will reduce sensitivity and result in difficult to interpret changes in PET signals.

To reduce the susceptibility of TK2 to dTTP-mediated feedback inhibition, we took advantage of the 40% sequence identity between human TK2 and *Drosophila melanogaster* deoxyribonucleoside kinase (Dm-DNK) (53) and of the identification of a point mutation (N64D) in Dm-DNK that has been shown to reduce the effect of dTTP feedback inhibition (54). The residue in TK2 corresponding to Asn-64 in *D. melanogaster* deoxyribonucleoside kinase is Asn-93; the corresponding mutation in TK2 is N93D. To predict the effects of the N93D mutation on the structure of TK2, we used molecular modeling. We took advantage of the fact that dCK belongs to the same family of nucleoside kinases as TK2. The sequence identity and homology between dCK and TK2 are 35 and 50%, respectively. Based on our previous work with dCK (28, 29), we obtained a homology model of TK2 (Fig. 2*A*). We hypothesized that, similar to dCK, TK2 will also adopt an open or a closed conformation. The enzyme is expected to be active in the closed conformation and inactive in the open conformation. In our model, when TK2 is in the closed conformation, Asn-93 is involved in hydrogen bonding with the glutamine at position 200 (*E200*, Fig. 2*A*). When the enzyme is in the open conformation, the residues are too far apart to interact. Thus, the N93D mutation would be expected to disfavor the closed conformation due to disruption of the interaction between Asn-93 and Glu-200 (Fig. 2*A*). dTTP should be able to exert its negative feedback inhibition on TK2 only if the enzyme is in the closed conformation. Because the N93D mutation favors the open conformation of the enzyme, we predicted there would be a reduced probability for dTTP to bind and exert its inhibitory effect.

To test this hypothesis we performed kinase assays using L-FMAU and recombinant WT TK2 and TK2-N93D in the presence of varying amounts of dTTP (Fig. 2*B*). WT TK2 activity decreased by 20% in the presence of 10 μM dTTP. In contrast, the activity of the N93D mutant decreased by only 4%. When the dTTP concentration was increased to 100 μM, the activity of WT TK2 decreased by 55%, whereas that of TK2-N93D decreased by less than 5%.

We then used cell-based uptake assays to determine whether the decreased susceptibility to feedback inhibition conferred by the N93D mutation increases L-^{18}F-FMAU uptake. As shown in Fig. 2*C*, we observed a 1.5-fold increase in L-^{18}F-FMAU uptake by the N93D TK2 expressing L1210 cells relative to cells expressing similar levels of WT TK2.

To confirm that the increase in signal can also be detected *in vivo*, we used mice implanted with L1210 cells transduced with the WT TK2 and mutant TK2-N93D PRGs (Fig. 2*D*). *In vivo*, L-^{18}F-FMAU uptake by TK2-N93D PRG-expressing cells was nearly double of that observed with the WT TK2-expressing cells (Figs. 2, *D* and *E*). Thus, by engineering a TK2 mutant that is less sensitive to feedback inhibition, we were able to improve the sensitivity of this candidate PRG for L-^{18}F-FMAU.

Further Improvements of Selectivity and Affinity of TK2-derived PRG for L-^{18}F-FMAU—For enzymatic PRGs, the higher the catalytic turnover (k_{cat}) of the enzyme, the more the PRP will accumulate per unit time, leading to a higher PET signal. We determined the k_{cat} of mutated TK2 PRG for L analogs compared with the endogenous substrate, D-dT. Relative to WT TK2, the N93D mutation reduced the k_{cat} of the enzyme

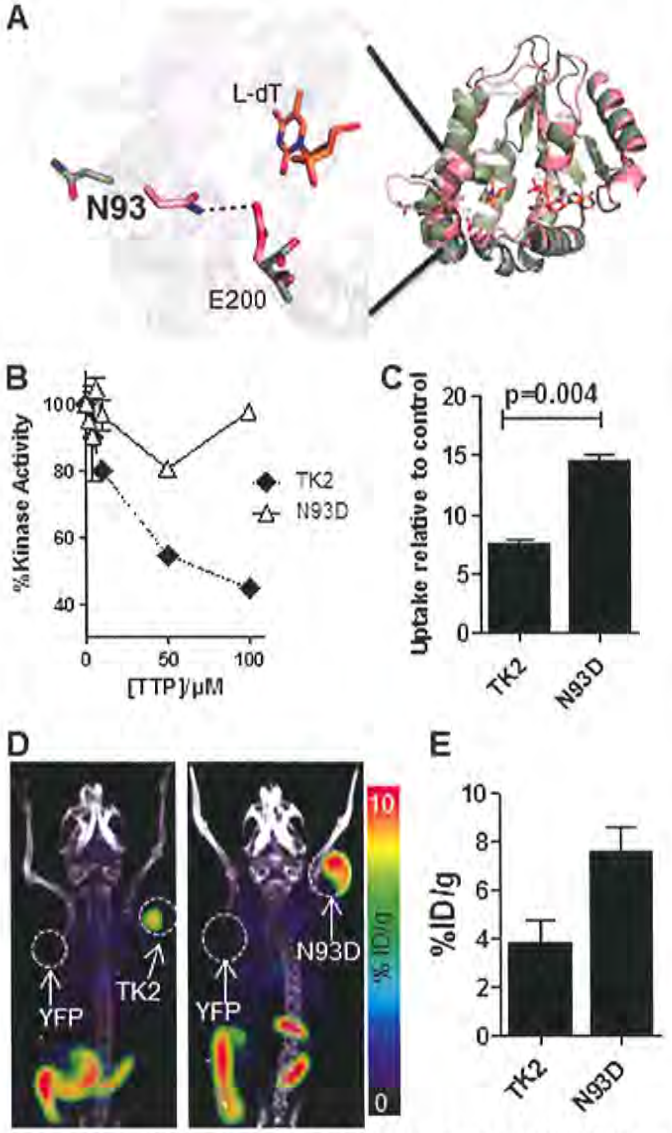

FIGURE 2. **Evaluation of the TK2-N93D mutant.** *A*, model of WT TK2 bound with L-dT in both the closed (*green*) and open (*pink*) conformation of the enzyme. ADP is bound in the phosphate donor pocket shown in this model. The enzyme is active in the closed conformation, which is stabilized by bonds between residues Asn-93 and Glu-200. When asparagine 93 is mutated to a glutamine, the bonds are disrupted, and the enzyme is predicted to switch to an open (inactive) conformation. *B*, L-FMAU kinase assay using recombinant WT TK2 and TK2-N93D in the presence of increasing concentrations of dTTP is shown. *C*, L-^{18}F-FMAU uptake assay using WT TK2- or TK2-N93D-expressing L1210 cells is shown. Probe uptake values are reported relative to a control L1210 cell line that expresses YFP. Results are for a representative experiment or $n = 2$ experiments. *D*, L-^{18}F-FMAU microPET/CT scans of mice bearing L1210 tumors engineered to express various PRGs (*TK2*, L1210-TK2; *N93D*, L1210-TK2-N93D; *YFP*, L1210-YFP). *E*, shown is quantification of PET scans from *panel D*. *%ID/g*, % injected dose/g.

toward D-dT, L-dT, and L-FMAU (Table 1). However, the activity toward D-dT decreased by 77%, whereas that for L-dT and L-FMAU decreased only 48 and 32%, respectively. The k_{cat} (L-FMAU)/k_{cat} (D-dT) ratio for N93D nearly triples when compared with wild type. k_{cat}/K_m gives a measure of the substrate preference of an enzyme. Compared with WT TK2, the k_{cat}/K_m of N93D for L-FMAU increased by 77%, whereas the k_{cat}/K_m for D-dT decreased by 60%. Thus, the N93D mutation also achieved the goal of increasing the preference of the enzyme for L-FMAU over the natural substrate.

To identify additional mutations that may further improve the selectivity of the TK2 PRG for L analogs, high resolution structures of dCK in complex with L and D substrates (55) were used to generate a homology model of TK2 with bound L-dT and D-dT (Fig. 3*A*). We then used this model to identify residues that, when mutated, would result in an enzyme with increased affinity for L-dT and decreased affinity for D-dT. This approach led to the identification of residue Leu-109 (Fig. 3*A*). According to our homology model, this residue interacts with the pyrimidine base. We surmised that if Leu-109 were mutated to an amino acid with a bulkier side chain (*e.g.* phenylalanine), this would induce a steric clash with D nucleosides but less so with L nucleosides. In turn, this would lead to preferential binding of L *versus* D nucleosides. Contrary to our expectations, the L109F mutation led to a decrease in the K_m for both the D and L forms of dT (Table 1). Notably, the L109F mutation made the enzyme faster at phosphorylating all of the substrates tested, with a bigger effect on D-dT. Thus, for WT TK2, the k_{cat} (L-FMAU)/k_{cat} (D-dT) ratio is 3.7, whereas for TK2-L109F this is 2.4 (Table 1). Compared with WT TK2, the k_{cat}/K_m of L109F for L-FMAU increased 2.4 times, whereas the k_{cat}/K_m for D-dT increased 6.7 times. Thus, contrary to the prediction, the L109F mutation increased the preference of the enzyme for D-dT compared with L-FMAU. This demonstrates that although a homology model can be sufficient to identify "hot spots" for mutagenesis (in this case, position 109), such a model may lack accuracy that can only be attained by an experimentally derived model. Nevertheless, although the L109F did not provide the desired increase in selectivity toward L nucleosides, it is important to note that the L109F mutation did increase the overall speed of the enzyme for all tested substrates.

Based on these observations, we generated TK2-N93D/L109F with the expectation that this double mutant will combine the enzymatic properties of the two single mutants. As shown in Table 1, this was indeed the case. Compared with TK2, the N93D/L109F double mutant had decreased k_{cat} with D-dT (down 49%) but increased k_{cat} with L-dT (up 54%) and L-FMAU (up 100%). The k_{cat} (L-FMAU)/k_{cat} (D-dT) ratio for the TK2-N93D/L109F mutant is 14.9, 4-fold higher than that for TK2 and nearly 40% higher than that for TK2-N93D. Importantly, the TK2-N93D/L109F mutant still retained resistance to inhibition by dTTP (Fig. 3*B*). In the presence of 10 μM dTTP, the kinase activity of recombinant TK2-N93D/L109F decreased by only 4%, whereas that of TK2-L109F decreased by 25%. At 100 μM dTTP, TK2-N93D/L109F decreased by only 11%, whereasTK2-L109F decreased by 56%.

To determine the preference of the TK2 mutants for L-^{18}F-FMAU over D-dT, we performed uptake assays using L1210 cells in the presence or absence of 5 μM D-dT (Fig. 3*C*). L-^{18}F-FMAU uptake by TK2-N93D/L109F-expressing L1210 cells in the absence of D-dT was >1.5 times higher than that of TK2-N93D cells and nearly 4 times higher than that of TK2-L109F cells. In the presence of 5 μM D-dT, L-^{18}F-FMAU uptake by TK2-N93D/L109F cells decreased by 47%, whereas that of TK2-N93D cells decreased by 75%. Although the L-^{18}F-FMAU uptake of TK2-L109F in the presence of 5 μM D-dT decreased

TABLE 1
Kinetic analyses of recombinant TK2 mutants with D-dT, L-dT, and L-FMAU
Values were measured at 37 °C using 1 mM ATP as phosphoryl donor. k_{cat} is in s^{-1}, K_m is in μM, and k_{cat}/K_m is in $M^{-1} \times s^{-1}$.

Nucleoside		WT	N93D	L109F	N93D/L109F
D-dT	k_{cat}	0.123 ± 0.002	0.029 ± 0.001	0.459 ± 0.005	0.063 ± 0.001
	K_m	14.6 ± 0.9	8.9 ± 1.3	8.2 ± 0.6	9.8 ± 0.7
	k_{cat}/K_m	$8.42\ 10^{-3}$	3.26×10^{-3}	55.98×10^{-3}	6.43×10^{-3}
L-dT	k_{cat}	0.370 ± 0.012	0.195 ± 0.003	1.176 ± 0.033	0.572 ± 0.012
	K_m	66.9 ± 7.5	18.2 ± 1.4	34.1 ± 3.9	17.4 ± 1.8
	k_{cat}/K_m	5.53×10^{-3}	10.71×10^{-3}	34.49×10^{-3}	32.87×10^{-3}
L-FMAU	k_{cat}	0.461 ± 0.016	0.316 ± 0.009	1.079 ± 0.026	0.940 ± 0.026
	K_m	37.6 ± 5.2	14.5 ± 2.1	36.7 ± 3.8	66.0 ± 6.3
	k_{cat}/K_m	12.26×10^{-3}	21.79×10^{-3}	29.40×10^{-3}	14.24×10^{-3}
Ratio k_{cat} (L-FMAU/D-dT)		3.7	10.9	2.4	14.9

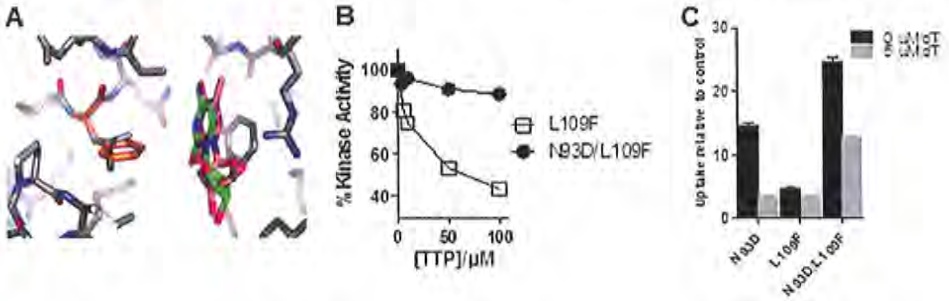

FIGURE 3. **Evaluation of L109F and N93D/L109F TK2 mutants.** *A*, a homology model of TK2 bound with L-dT (*pink*) and dT (*green*) is shown. The TK2 model (*solid residues*) is overlaid on a crystal structure of dCK (*light colored residues*) with bound substrates. The TK2 residue Leu-109 is *highlighted in gold*. *B*, a L-FMAU kinase assay using recombinant TK2-L109F and TK2-N93D/L109F in the presence of increasing dTTP concentrations is shown. *C*, shown is an *in vitro* L-^{18}F-FMAU uptake assay using L1210 cells expressing either TK2-N93D, TK2-L109F, or TK2-N93D/L109F. The assay was done in either the presence or absence of 5 μM D-dT. Probe uptake values are reported relative to a control L1210 cell line that expresses YFP. Results are for a representative experiment or $n = 2$ experiments. $p = 0.005$ between N93D and N93D/L109F in the presence of 0 μM dT, and $p = 0.0008$ between N93D and N93D/L109F in the presence of 5 μM dT.

by 37%, it was still only 31% of the corresponding uptake for TK2-N93D/L109F.

Next, we investigated whether TK2-N93D/L109F had low activity toward deoxycytidine, the other endogenous nucleoside that is phosphorylated by WT TK2. TK2-N93D/L109F has a k_{obs} (dC) that is 62% that of TK2 (supplemental Table 2). These data indicate that TK2-N93D/L109F is orthogonal to wild type TK2, with increased activity toward the L-^{18}F-FMAU PRP and decreased activity toward the endogenous nucleosides thymidine and deoxycytidine.

In Vivo Comparison between TK2-N93D/L109F/L-^{18}F-FMAU and HSV1-sr39tk/^{18}F-FHBG PRG-PRP Systems—Mice implanted with L1210 cells expressing TK2-based PRGs were scanned by microPET/CT using L-^{18}F-FMAU (Fig. 4*A*). For comparison, mice implanted with L1210 cells expressing HSV1-sr39tk were scanned by microPET/CT using ^{18}F-FHBG (Fig. 4*B*). L-^{18}F-FMAU uptake by the TK2-N93D/L109F-expressing L1210 cells was 2.6-fold higher than that of TK2-N93D-expressing cells (Fig. 4*C*). ^{18}F-FHBG accumulation into sr39tk-expressing L1210 cells was comparable with that of L-^{18}F-FMAU into L1210 cells expressing TK2-N93D/L109F (24.1 ± 6.2 *versus* 19.9 ± 1.5% injected dose/g; $p = 0.37$). Taken together, these findings demonstrate that the sensitivity of the TK2 N93D/L109F PRG is higher than that of the TK2-N93D PRG and is not significantly different from that of the sr39tk/^{18}F-FHBG pair.

L-^{18}F-FMAU Biodistribution in Humans—As the first step toward clinical translation of the newly developed PRG-PRP system, we determined the biodistribution of L-^{18}F-FMAU in humans. Fig. 5 illustrates the biodistribution of L-^{18}F-FMAU in two healthy volunteers and the biodistribution of ^{18}F-FHBG in a female volunteer 2 h post-administration of the PRPs. Mean standard uptake values of the probes in different tissues for ^{18}F-FHBG and L-^{18}F-FMAU are listed in supplemental Table 3. For both probes, relatively high signals were observed in liver, kidneys, gall bladder, bladder, and the GI tract. L-^{18}F-FMAU accumulation was also observed in the myocardium. At 2 h, more intense activity was observed in the liver after L-^{18}F-FMAU injections than after ^{18}F-FHBG administration. However, L-^{18}F-FMAU activity was lower than that of ^{18}F-FHBG within the GI tract region.

DISCUSSION

To develop a PRG that can be used in conjunction with L-^{18}F-FMAU, a thymidine analog with the unnatural L-conformation, we removed the mitochondrial sorting sequence in human TK2. As shown previously, the truncated protein is expected to localize in the cytosol rather than in the mitochondria (20). Rational design was then used to improve the sensitivity and selectivity of the TK2 PRG. This led to the development of TK2-N93D/L109F, a double mutant TK2 kinase characterized by reduced affinity for the natural substrates D-thymidine and D-deoxycytidine and increased affinity for L-FMAU. Studies in mice indicated that the TK2-N93D/L109F PRG has comparable sensitivity to that of the widely used HSV1-sr39tk/^{18}F-FHBG system. We have also determined the biodistribution of L-FMAU in humans.

Advantages of TK2-N93D/L109F/L-^{18}F-FMAU PRG System—In mice, L-^{18}F-FMAU accumulates in the liver 1-h post injection (data not shown). The progression of the signal from the liver to the gallbladder and then to the GI indicates that L-^{18}F-FMAU is excreted via a hepato-biliary mechanism, similar to

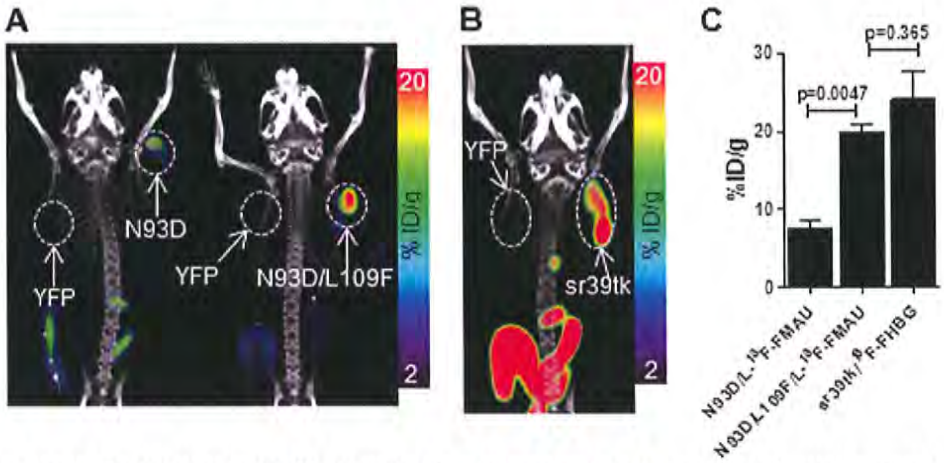

FIGURE 4. **Comparison of ΔTK2/L-^{18}F-FMAU and sr39tk/^{18}F-FHBG PET reporter gene systems.** *A*, shown are L-^{18}F-FMAU microPET/CT scans of mice bearing L1210 tumors engineered to express various TK2-based PRGs. *B*, shown are ^{18}F-FHBG microPET/CT scans of mice bearing L1210 tumors engineered to express sr39tk. *C*, shown is quantification of probe uptake in L1210 tumors from *A* and *B*. *%ID/g*, % injected dose/g.

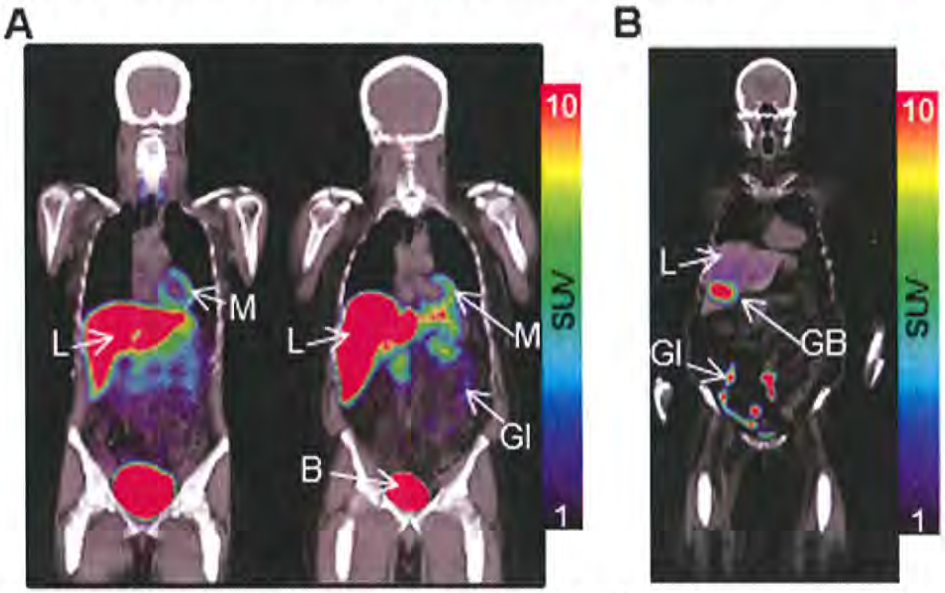

FIGURE 5. **Biodistribution of L-^{18}F-FMAU and ^{18}F-FHBG in humans.** PET/CT scans of a healthy female (*left*) and a healthy male (*right*) volunteer 2 h after injection of L-^{18}F-FMAU (*A*) and pretreatment glioma patient 2 h after injection of ^{18}F-FHBG (*B*). *B*, bladder; *GB*, gallbladder; *L*, liver; *M*, myocardium. *SUV*, standard uptake value.

that observed for ^{18}F-FHBG (12). However, the GI activity in L-^{18}F-FMAU-injected mice is significantly less intense than that observed in mice injected with ^{18}F-FHBG. The intense signal in the GI of mice injected with ^{18}F-FHBG leads to spillover in other organs in the lower abdomen, limiting the utility of ^{18}F-FHBG for cell tracking applications in mice if these cells localize in the abdominal cavity.

In addition to its human origin (which is expected to reduce immunogenicity compared with the viral PRGs), the TK2-N93D/L109F PRG also has the advantage of reduced activity toward the endogenous nucleosides, D-thymidine and D-deoxycytidine. PRGs are typically overexpressed in therapeutic cells. In this context, if the mutant PRG retains the ability to efficiently phosphorylate thymidine and/or deoxycytidine, then this may alter cellular metabolism due to overproduction of dTTP and/or dCTP. Such effects would be of particular concern in preclinical settings as serum levels of thymidine in mice and rats are 9–15 times higher than those in humans (56). Any changes in nucleotide metabolism and dNTP pools in therapeutic cells may have genotoxic consequences, especially when prolonged persistence *in vivo* of these cells is anticipated (for example in the case of stem cells). In contrast to previously reported PRG such as dCK-double mutant, TK2-N93D/L109F is less likely to perturb cellular nucleotide metabolism and genomic integrity due to the decreased activity of the double mutant enzyme toward natural substrates.

Disadvantages of New TK2-N93D/L109F/L-^{18}F-FMAU PRG System and Potential Improvements—The observed differences between the biodistribution of L-^{18}F-FMAU biodistribution in mice and humans underscore the importance of performing such comparative studies at an early stage of the development process for new PRG-PRP systems. In contrast to the excellent biodistribution in mice, in humans L-^{18}F-FMAU accumulates in the myocardium and liver. Regarding L-^{18}F-FMAU accumu-

lation in the heart, the myocardium has a very high density of mitochondria (57). Moreover, the reported activity of the WT mitochondrial TK2 enzyme from human heart tissue is nearly 10 times higher than that of the enzyme from mouse heart tissue (58, 59). This difference may explain the observed differences in L-^{18}F-FMAU myocardial accumulation between mice and humans. L-^{18}F-FMAU is taken up by the liver of both mice and humans. However, L-^{18}F-FMAU eventually clears the murine liver but is retained in the human liver. One reason for this difference may be that, similar to ^{18}F-FLT (3′-deoxy-3′-^{18}fluorothymidine) (60), L-^{18}F-FMAU may also undergo glucuronidation in human liver tissue. Glucuronidation of thymidine analogs is significantly less extensive in mice than in humans (61). Given the accumulation of L-^{18}F-FMAU in human liver and myocardium, this probe may not be useful for PET imaging of therapeutic cells at these sites. Myocardial accumulation may be reduced if L-^{18}F-FMAU is modified to decrease its phosphorylation by WT TK2. Replacing the 5-methyl group with a larger substituent such as ethyl or propyl may achieve this objective.

Conclusion—New PET reporter gene/probe systems are needed to assist the development and clinical translation of cell-based therapies. In the current study we used a structure-guided approach to develop a human nucleoside kinase-based PRG characterized by high specificity and selectivity for L-^{18}F-FMAU, a non-natural nucleoside analog PRP. The initial findings in mice and the observed biodistribution of L-^{18}F-FMAU in mice and humans warrant additional studies in both species and suggest potential strategies to further improve the sensitivity and specificity of the new human TK2-based PET reporter gene assay.

Acknowledgments—We thank Lisa Ta for excellent technical assistance. We thank Liu Wei and Larry Pang for assistance with micro-PET/CT imaging and the cyclotron group for producing the PET probes used in this study.

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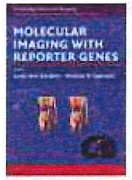
CELL KINETICS
- Direct Labeling
- Genetic Engineering

REPORTER GENE IMAGING
- Fluorescence
- Bioluminescence
- Positron Emission Tomography (PET)
- Clinical Imaging
- References



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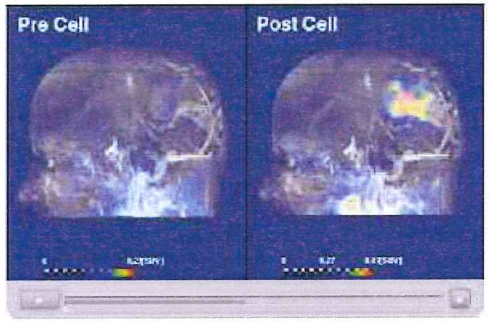
TECHNOLOGY

CellSight allows therapy developers to "barcode" their cells or genes prior to introduction into living subjects (including humans) and then view these "barcoded" cells or genes at various time points after treatment. Information can be gathered not only for the injected therapeutic cells but also their progeny in the living subject.



This video illustrates PET reporter gene based imaging of therapeutic cells in the brain of a glioma patient. The PET image is superimposed over the brain MRI, showing the location and intensity of the PET reporter imaging probe [18F]FHBG before and after injection of HSV1-tk expressing cytolyticT cells.

CELL KINETICS DATA THAT CAN BE OBTAINED AT MULTIPLE TIME POINTS

- Cell Locations
- Cell Quantity at each Location
- Cell Survival
- Cell Proliferation
- Cell Status and Characteristics

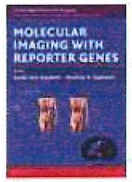
PROVEN METHODS TO IMAGE CELL KINETICS

- Direct Labeling with an Imaging Probe
- Genetic engineering of cells to express imaging reporter genes

METHODS TO PERFORM REPORTER GENE IMAGING IN LIVING SUBJECTS INCLUDE

- Fluorescence
- Bioluminescence

References



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PROVEN METHODS TO IMAGE CELL KINETICS

- Direct Labeling with an Imaging Probe
- Genetic engineering of cells to express imaging reporter genes

METHODS TO PERFORM REPORTER GENE IMAGING IN LIVING SUBJECTS INCLUDE

- Fluorescence
- Bioluminescence
- Positron Emission Tomography (PET)

CellSight Technologies provides means to combine the three methods of gene imaging with a single tri-fusion multimodality reporter gene. You can then track implanted cells or genes from preclinical applications and then translate to clinical applications.

PET allows imaging in both small and large animals, a technique translatable to imaging in humans.

CellSight personnel have been granted FDA "Investigational New Drug" (IND) to image PET reporter gene expression in patients using [18F]FHBG. This is the only FDA approved molecular imaging probe to image cells in humans.

Therapy developers can use the same triple fusion gene during therapy development for imaging cells in vitro all the way to imaging living subjects.

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EXHIBIT B
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AC-CS001295

CellSight Technologies, Inc.

Imaging Therapeutics

- **Cell Kinetics**
  - Direct Labeling
  - Genetic Engineering
- **Reporter Gene Imaging**
  - Fluorescence
  - Bioluminescence
  - Positron Emission Tomography (PET)
  - Clinical Imaging
  - References

Order Molecular Imaging with Reporter Genes

Technology

CellSight allows therapy developers to "barcode" their cells or genes prior to introduction into living subjects (including humans) and then view these "barcoded" cells or genes at various time points after treatment. Information can be gathered not only for the injected therapeutic cells but also their progeny in the living subject.

Cell Kinetics data that can be obtained at multiple time points

- Cell Locations
- Cell Quantity at each Location
- Cell Survival
- Cell Proliferation
- Cell Status and Characteristics

Proven methods to image Cell Kinetics

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Methods to perform reporter gene imaging in living subjects include

- Fluorescence
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